COUNTWAY LIBRARY
HC 3IDK /

BOSTON MEDICAL LIBRARY
IN THE
FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE

Digitized by the Internet Archive
in 2017 with funding from
The National Endowment for the Humanities and the Arcadia Fund

https://archive.org/details/westernjournalo1201cali_0

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON
MAR 12 1974

THE WESTERN Journal of Medicine

VOLUME 120 • NUMBER 1 **JANUARY 1974**

1 *Forty-Day Fever—An Epidemic of Cytomegalovirus Disease in a Renal Transplant Population*
ALAN S. COULSON, MA, MB, PhD, ZOLTAN J. LUCAS, MD, MERCY CONDY, RN, and ROY COHN, MD

8 *Pulmonary Complications of Drug Abuse* LEON S. GOTTLIEB, MD, and THOMAS C. BOYLEN, MD

17 *Mixed Mesodermal Tumors of the Uterus* JOSE F. AFONSO, MD

27 *Acupuncture and Its Role in Modern Medicine* ANDREW J. LEWIN, MD

MEDICAL PROGRESS

33 *Current Concepts of Sodium Chloride and Water Transport by the Mammalian Nephron*
PAUL F. MERCER, PhD, DAVID A. MADDOX, PhD, and BARRY M. BRENNER, MD

MEDICAL STAFF CONFERENCE

46 *Syphilis* Discussion by MARCUS A. CONANT, MD

SPECIALTY CONFERENCE

55 *Potpourri of Adenoviral Infections*
Participants: JAMES D. CONNOR, MD, RICHARD M. BUCHTA, MD, FRANK DeGENARO, JR., MD, MARY ANN FLETCHER, MD, and WILLIAM L. NYHAN, MD, PhD
From the Department of Pediatrics, Division of Pediatric Infectious Diseases, University Hospital of San Diego County and the University of California, San Diego, School of Medicine

62 IMPORTANT ADVANCES IN CLINICAL MEDICINE—*Otolaryngology*

67 EDITORIALS • *A Voice for Medicine in the West* • *The Ubiquitous Adenovirus* • *Cigarette Smoking Ten Years Later* • *Emergency Medicine*

CASE REPORTS

72 *Sternal-Costal Infection with Pseudomonas—A Complication of Drug Abuse* THOMAS F. KEYS, MD

74 *Congenital Contractural Arachnodactyly*
MEREDITH S. HALE, MD, HOWARD D. RODMAN, MD, and JACK LIPSHIN, MD

77 LETTERS TO THE EDITOR

SPECIAL ARTICLES

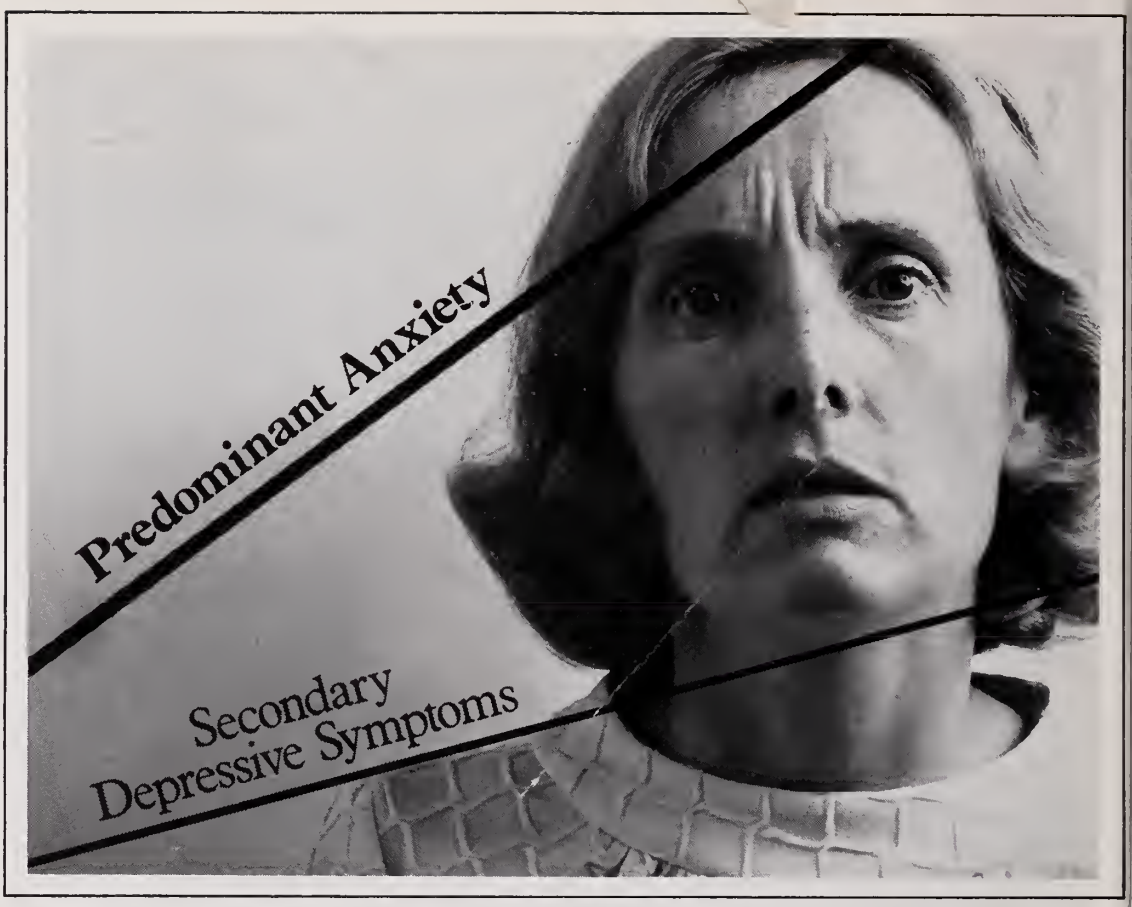
80 *A Review of Mandatory Continuing Medical Education in Oregon* MERLE PENNINGTON, MD

88 *The Makings of Policy for Medicine and Health—A Report on the Institute of Medicine*
JOHN R. HOGNESS, MD

92 *Traumatic Injury—A Health Care Crisis*
DONALD D. TRUNKEY, MD, ROBERT C. LIM, JR., MD, and F. WILLIAM BLAISDELL, MD

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA; OREGON; WASHINGTON, MONTANA, AND ALASKA**
(See Advertising Page 35)

01%-EXC 122973 SUB050020010
NEW ENG JRL MED
10 SHATTUCK
BOSTON MA 02115



This psychoneurotic
often responds

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON

MAR 1 2 1974

When you determine that the depressive symptoms are associated with or secondary to predominant anxiety in the psychoneurotic patient, consider Valium (diazepam) in addition to reassurance and counseling, for the psychotherapeutic support it provides. As anxiety is relieved, the depressive symptoms referable to it are also often relieved or reduced.

The beneficial effect of Valium is usually pronounced and rapid. Improvement generally becomes evident within a few days, although some patients may require a longer period. Moreover, Valium (diazepam) is generally well tolerated. Side effects most commonly reported are drowsiness, ataxia and fatigue. Caution your patients against engaging in hazardous occupations or driving.

Frequently, the patient's symptoms are greatly intensified at bedtime. In such situations, Valium offers an additional advantage: adding an *h.s.* dose to the *b.i.d.* or *t.i.d.* schedule can relieve the anxiety and thus may encourage a more restful night's sleep.

symptom complex to Valium® (diazepam)

Precautions: If combined with ther psychotropics or anticonvul- ants, consider carefully pharma- ology of agents employed; drugs ich as phenothiazines, narcotics, arbiturates, MAO inhibitors and ther antidepressants may poten- ate its action. Usual precautions idicated in patients severely de- ressed, or with latent depression, with suicidal tendencies. Observe sual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

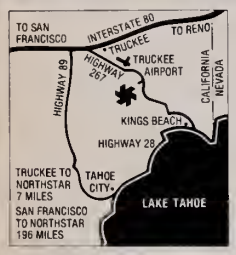
Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

Valium® 2-mg, 5-mg, 10-mg tablets
(diazepam)

Ski in. Ski out.



To: Northstar
P.O. Box 129
Truckee,
Calif. 95734

☐ Please send me more information about Northstar at Tahoe.

I am specially interested in

☐ homesites
☐ condominiums
☐ skiing

Name

Address

City State Zip

Telephone Number

(WJM)012 1/74

For more information about Northstar's Ski Trail Condominiums, call **toll free (800) 852-7507.** Or send us this coupon.

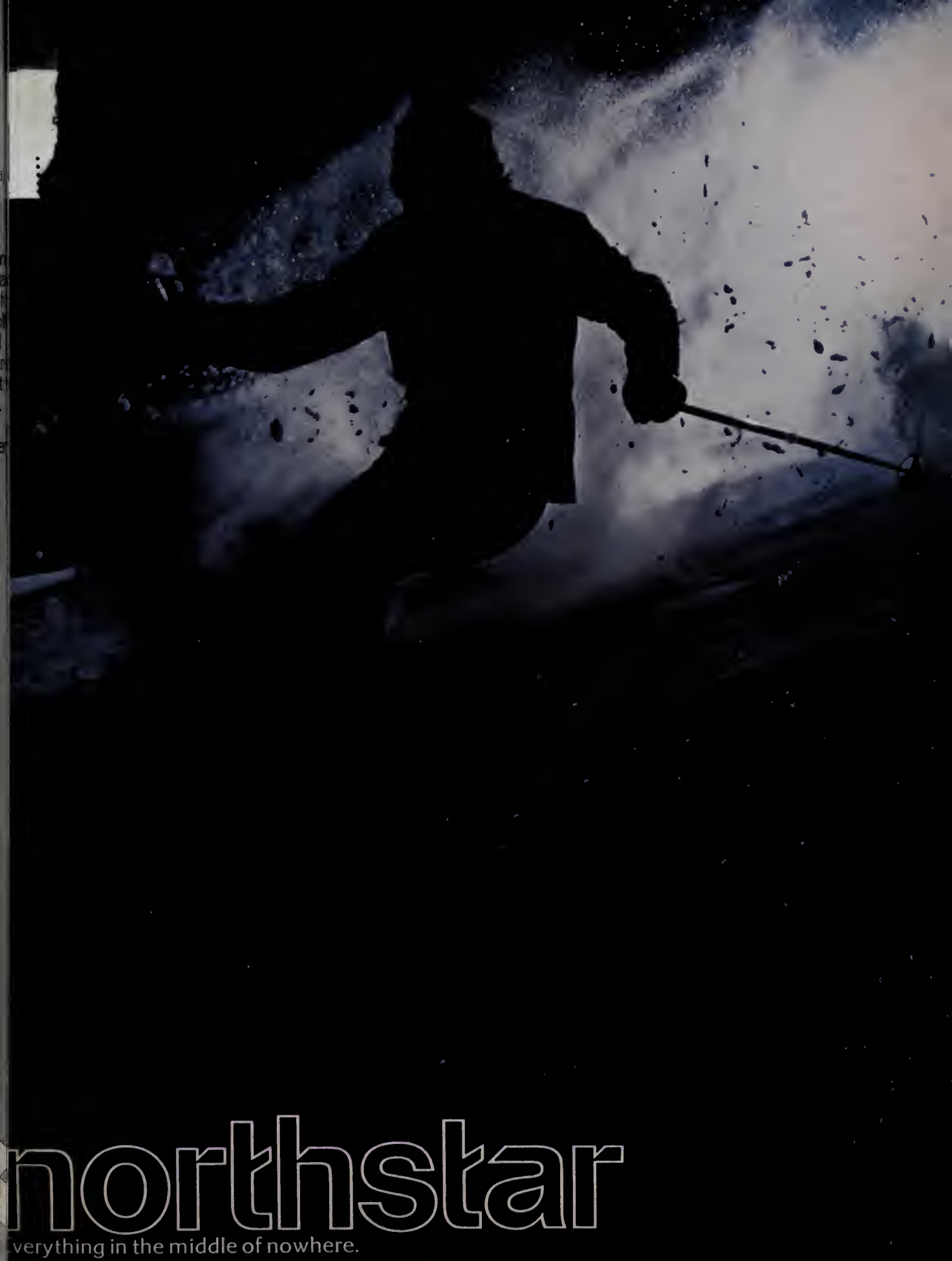
If you spend more time getting to the ski slopes than you spend skiing, that's no fun. And we know it. So, at Northstar, unlike other ski resorts, we've planned a new group of condominiums that put the fun back in skiing. Because the slopes are right outside the door. They're wind protected, pine sheltered. And the snow conditions are excellent. You can ski out in the morning and ski home at night. Simple. And lots of fun.

These new condominiums are called Ski Trail. And like everything at Northstar, they've been carefully planned with comfort and convenience in mind. Skiing in and skiing out is only the beginning. A short walk will take you to Northstar Village and Northstar's private off-the-slopes recreational complex. Where you'll find exercise rooms, saunas and a whirlpool bath. What could be nicer after a day on the mountain?

And the fun doesn't end when the winter's over. Summertime at Northstar is the tim for tennis, hiking, swimming a riding. Clearing is completed fo our 18-hole championship goll course. And construction will begin soon. All the facilities are very nearby. All very private, to

Ski Trail Condominiums. They really do put you in the middle of everything. Summer and winter.

A development of Trimont Land Company, a wholly owned subsidiary of Fibreboard Corporation.


northstar
verything in the middle of nowhere.

THE WESTERN Journal of Medicine

Since 1902 • Formerly California Medicine

OWNED AND PUBLISHED BY THE CALIFORNIA MEDICAL ASSOCIATION
731 MARKET ST. • SAN FRANCISCO, CA 94103 • TELEPHONE (415) 777-2000

editorial communications to:
MALCOLM S. M. WATTS, M.D., *Editor*

business communications to:
LYTTON O. HETLAND, *Business Manager*

. . .

LLOYD H. SMITH, JR., M.D., *Associate Editor*
ROBERT F. EDWARDS, *Managing Editor*
DAVID GREER, *Associate Managing Editor*

Editorial Board

Chairman of the Board
Malcolm S. M. Watts, San Francisco

Allergy
Norman Shure, Los Angeles
Abba I. Terr, San Francisco

Anesthesiology
Ronald L. Katz, Los Angeles

Dermatology
George F. Odland, Seattle
Rees B. Rees, San Francisco
Richard B. Stoughton, La Jolla

General and Family Practice
Robert L. Hippen, San Diego
Herbert A. Holden, San Leandro

General Surgery
Frederick M. Anderson, Reno
Richard E. Gardner, San Francisco
Lucius D. Hill, Seattle

Industrial Medicine and Toxicology
Thomas H. Milby, Berkeley

Internal Medicine
Robert J. Bolt, Davis
J. David Bristow, Portland
Marcus A. Krupp, Palo Alto
Robert G. Petersdorf, Seattle
Donald W. Petit, Los Angeles
Edgar Wayburn, San Francisco
Nathan J. Zvaifler, San Diego

Neurology
Pierre M. Dreyfus, Davis
Robert A. Fishman, San Francisco
Phillip D. Swanson, Seattle

Obstetrics and Gynecology
Ralph C. Benson, Portland
William J. Dignam, Los Angeles
Ernest W. Page, San Francisco

Ophthalmology
David O. Harrington, San Francisco
Robert S. Hepler, Los Angeles

Orthopedics
Rodney K. Beals, Portland
John A. Blosser, Oakland
Paul E. McMaster, Beverly Hills

Otolaryngology
Mansfield F. W. Smith, San Jose
Paul H. Ward, Los Angeles

Pathology
Richard L. Kempson, Stanford
Averill A. Liebow, San Diego

Pediatrics
Robert E. Greenberg, Los Angeles
William L. Nyhan, San Diego
Henry R. Shinefield, San Francisco
Paul F. Wehrle, Los Angeles

Pharmacology
Sydney M. Finegold, Los Angeles
Kenneth L. Melmon, San Francisco

Physical Medicine and Rehabilitation
Elizabeth S. Austin, Los Angeles
Glenn G. Reynolds, San Jose

Plastic Surgery
Richard L. Dakin, San Rafael
N. John Wilde, Fresno

Psychiatry
Carl Eisdorfer, Seattle
Leon J. Epstein, San Francisco
George L. Mallory, Los Angeles
Helen Tausend, Los Angeles

Public Health
J. M. Stubblebine, Sacramento
Irma M. West, Sacramento

Radiology
H. Joachim Burhenne, San Francisco
Robert B. Engle, Pasadena
Melvin M. Figley, Seattle

Thoracic and Cardiac Surgery
John E. Connolly, Irvine
Albert Starr, Portland

Urology
Thomas F. Conroy, San Mateo
Ruben F. Gittes, La Jolla

Consultants in Medical Services and Health Care
Gerald A. Besson, Sunnyvale
Paul Scholten, San Francisco

Policy Committee—Editorial Board

THOMAS N. ELMENDORF ..... Willows
STANLEY A. MOORE ..... San Diego
JOSEPH F. BOYLE ..... Los Angeles
HENRY V. EASTMAN ..... Tustin
E. KASH ROSE ..... Napa
HELEN B. WEYRAUCH ..... San Francisco
MALCOLM S. M. WATTS ..... San Francisco

Advertisements—THE WESTERN JOURNAL OF MEDICINE is published the first week of each month. Advertising copy must be received not later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee.

SALES REPRESENTATIVES: JOHN H. HARLING, INC.

EAST:
SAUL HORNIK
655 AMBOY AVENUE
WOODBRIDGE, N.J. 07095
TEL. (201) 636-7150

MIDWEST:
JOHN HARLING • JAMES ANTON
18 SO. MICHIGAN AVE.
CHICAGO, ILL. 60603
TEL. (312) 641-0755

WEST: MELVIN B. TYLER
731 MARKET ST.
SAN FRANCISCO, CA. 94103
TEL. (415) 777-2000

Copyright, 1974, by the California Medical Association.

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the non-commercial purpose of scientific or educational advancement.

Subscription prices, $8 ($9 for foreign countries); student subscription $4; single copies 80 cents.

Volumes begin with the first of January and the first of July. Subscriptions may commence at any time.

Change of Address—Requests for change of address should give both the old and new address.

CONTRIBUTIONS OF SCIENTIFIC AND ORIGINAL ARTICLES

Responsibilities for Statements and Conclusions in Original Articles—Authors are responsible for all statements, conclusions and methods of presenting their subjects. These may or may not be in harmony with the views of the editorial staff. It is aimed to permit authors to have as wide latitude as the general policy of the Journal and the demands on its space may permit. The right to reduce, revise or reject any manuscript is always reserved.

Exclusive Publication—Articles are accepted for publication on condition that they are contributed solely to this Journal. Ordinarily contributors will be notified within 60 days if a manuscript is accepted for publication. Every effort will be made to return unused manuscripts.

Length of Articles—Ordinarily articles should not exceed 3,000 words (approximately 5 printed pages). Under exceptional circumstances only will articles of over 4,000 words be published.

Manuscripts—Manuscripts should be typewritten, double spaced and the original typescript plus one copy submitted.

Illustrations—Ordinarily publication of 2 or 3 illustrations accompanying an article will be paid for by THE WESTERN JOURNAL OF MEDICINE. Any number beyond this might have to be paid for by the author.

References—Should conform to the following order: name of author, title of article, name of periodical, with volume, inclusive pages, month and year—i.e.: Lee GS: The heart rhythm following therapy with digitalis—In theory and practice. Arch Int Med 44:554-562, Dec 1942. They should be listed in the order in which they are cited in the text, numbered in sequence and punctuated as above.

Reprints—Reprints must be paid for by the author at established standard rates.

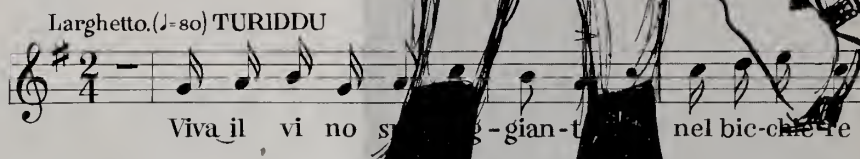
CONTRIBUTIONS OF "LETTERS TO THE EDITOR"

The Editorial Board will be glad to receive and consider for publication letters containing information of general interest to physicians or presenting constructive criticisms on issues of the day.

"Entered as second class matter at the post office in San Francisco and additional mailing offices under the Act of March 3, 1879." Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized August 10, 1918.

He knew what wine can do and so should you

CARUSO BY CARUSO: As himself, above, and as Turiddu in Cavalleria Rusticana, right.



Caruso caricatures reproduced by permission of Michael Sisca and La Follia di New York.

Enrico Caruso, winegrower and amateur sketch artist, was a sensation almost from the moment of his debut in traditional opera – at Caserta, Italy in April 1895 – singing *Viva il vino* in the role of *Turiddu* in *Cavalleria Rusticana* . . .

Long live wine . . .
Sparkling in its glass
Like a lover's laughter . . .

Caruso himself – impulsive, affectionate, volatile – learned moderation and wisdom in wine from his Neapolitan childhood (b. Naples, 1873; d. Naples, 1921). To him wine was a food, a daily companion, a pledge of fellowship and hospitality, a builder of morale and inducer to restful sleep, the world's gentlest tranquilizer – all the things modern medical research has been showing wise physicians and nurses for their own well-being and their patients' better care and convalescence.

Caruso Shook San Francisco – In his short lifetime (48 years) Caruso did 607 performances at the New York Met which adored him. His debut there in 1903 shook the music world – but his debut in San Francisco three years later, in 1906, was earthshaking in another way (otherwise, he might well have become a California winegrower, as Paderewski did). After singing *Don José* in *Carmen* at the Grand Opera House the night of April 17th, Caruso went to sleep at the Palace Hotel, and shortly thereafter – 5:12 a.m., Wednesday, April 18, 1906 – was catapulted from his bed, and from California, by the great San Francisco Earthquake and Fire. He paused only long enough to sketch the city in flames for a local paper – then, clutching a big photo of President Roosevelt which Teddy had given him only the week before, he departed, muttering "Give me Vesuvius!"

It was in Tuscany that Caruso grew his wine, at *Villa Bellosguardo,* his estate overlooking Florence and the Arno, in the lovely rolling countryside. There, in 1918, he installed his young New York bride, Dorothy, amid his teeming family and retinue. In a fascinating biography* of her Rico, Dorothy observes plaintively, "There were twenty-one people living with us."

Physically, this musical giant was a specimen to intrigue any physician. Chunky, five feet nine. A great head, with retentive brain (67 operatic roles, 500 songs). A great heart *(appassionata).* A big mouth, so perfectly domed inside *(risonante)* that he could close it over a raw egg without harming the shell. Lungs like bellows *(fortissimo),* which he could expand nine inches, holding a note so long *(sostenuto)* before bravura scale, that he often worried his audience!

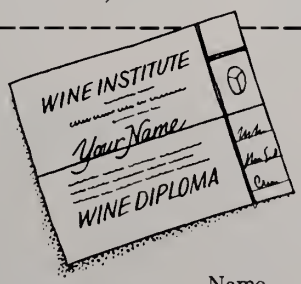
Immortal Voice – No wonder the legend grew, that he liked to shatter wineglasses by singing into them. Dorothy denies this.* The record shows that he had much respect for wine, women, and song. He took his pleasure instead in wine at meals with admiring friends, in his Dorothy and baby Gloria . . . and in song! His incomparable voice, "primitively" recorded between 1903 and 1920, still makes him the world's best-selling classic vocalist today . . .

If you would care for more reading about people and wine, and what it can do for your patients and your home pleasure, just fill out and mail us the coupon below.

– THE WINEGROWERS OF CALIFORNIA

*Enrico Caruso, His Life and Death, by Dorothy Caruso; © 1945, Simon & Schuster, N.Y.

HOW TO BECOME A "WINE EXPERT"



This Year We Offer to the physician, or member of his or her hospital or nursing staff or immediate family:

"WINE STUDY COURSE." Free. This is actually our 50-page, fact-filled booklet, "THE STORY OF WINE." Tells you all about wine and wine types, how made, how served, wine's fascinating history, etc. With it comes a short WINE QUESTIONNAIRE. After pleasant "studying" you quiz yourself and – if you wish – mail in your answers to us. If you pass (we're sure you will), you are a "wine expert," and to prove it we send you, also free, the little WINE DIPLOMA shown here.

"USES OF WINE IN MEDICAL PRACTICE" (A SUMMARY), also free, is our 64-page report based on recent worldwide scientific research on wine in therapy and patient care. Introduction by Russel V. Lee, M.D., noted geriatrics editor; Indications and Contraindications; Chemistry, Nutrition, Pharmacology; Wine in Hospitals and Nursing Homes; valuable Bibliography. Belongs on your bookshelf, or associate's.

WINE INSTITUTE, CM-2
717 Market Street, San Francisco, CA 94103

Kindly enroll me without cost or obligation in your famous *Wine Study Course* and send me also the free booklet *Uses of Wine in Medical Practice.* (Please print name carefully, and title, if desired, for Diploma purposes):

Name _____

Title _____

Address _____

City _____

State _____ ZIP _____

A NEW INJECTABLE ANTIBIOTIC

Please see last page for prescribing information.

Lilly introduces a new cephalosporin

Kefzol™

cefazolin sodium

Ampoules, equivalent to 250 mg., 500 mg., and 1 Gm. of cefazolin

Its major areas of indication:

respiratory tract infections

due to susceptible strains of *Diplococcus pneumoniae, Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci (Injectable benzathine penicillin is considered to be the drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.)

genito-urinary tract infections

due to susceptible strains of *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of *Enterobacter* and enterococci

skin and soft-tissue infections

due to susceptible strains of *Staph. aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci

See prescribing information for additional indications and susceptible organisms.

Some of its major features:

therapeutic serum levels

peak serum levels of 37.9 and 63.8 mcg./ml. respectively were obtained one to two hours following 500-mg. and 1-Gm. I.M. doses of cefazolin

antibacterial urinary concentrations

peak urine concentrations of approximately 2,400 and 4,000 mcg./ml. respectively were obtained following I.M. doses of 500 mg. and 1 Gm.

bile and synovial-fluid levels

levels approximately one-half those of serum concentrations

flexibility of administration

usual adult dosage—500 mg. to 1 Gm. t.i.d. or q.i.d.

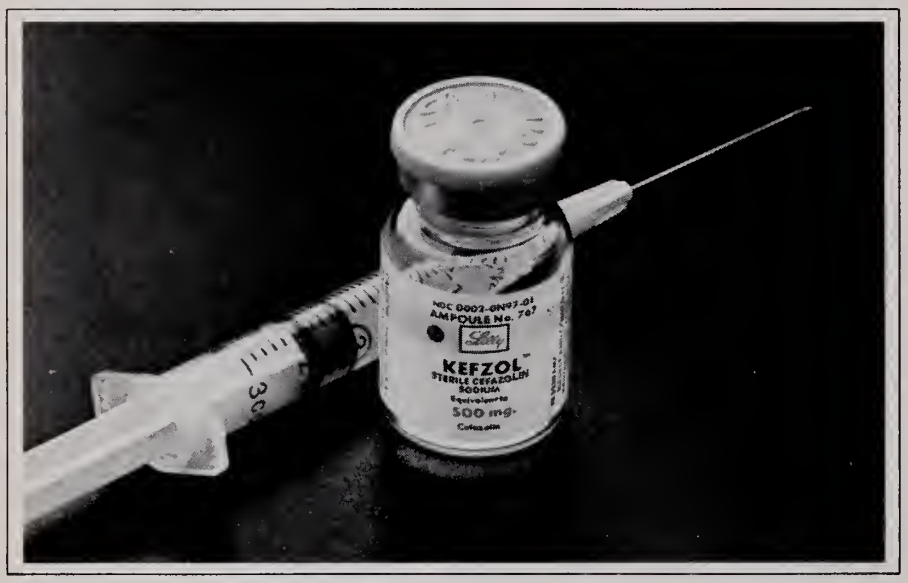
Kefzol is contraindicated in patients with known allergy to cephalosporins and should be given with great caution to penicillin-allergic patients.

Please see following page for summary of prescribing information.

301623

Kefzol™
cefazolin sodium

a new injectable antibiotic



Description: Kefzol™ (cefazolin sodium, Lilly) is a semisynthetic cephalosporin for parenteral administration. It is the sodium salt of 3-[[(5-methyl-1,3,4-thiadiazol-2-yl) thio]methyl]-8-oxo7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

Actions: *Microbiology*— In-vitro tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell-wall synthesis. Kefzol is active against the following organisms in vitro:

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Diplococcus pneumoniae
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole-positive *Proteus (Pr. vulgaris, Pr. morganii, Pr. rettgeri)* are resistant. Methicillin-resistant staphylococci, *Serratia, Pseudomonas, Mima,* and *Herellea* species are almost uniformly resistant to cefazolin.

Indications: Kefzol is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *D. pneumoniae, Klebsiella* species, *H. influenzae, Staph. aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci

Injectable benzathine penicillin is considered to be the drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

Kefzol is effective in the eradiction of streptococci from the nasopharynx; however, data establishing the efficacy of Kefzol in the subsequent prevention of rheumatic fever are not available at present.

Genito-urinary tract infections due to *Esch. coli, Pr. mirabilis, Klebsiella* species, and some strains of *Enterobacter* and enterococci

Skin and soft-tissue infections due to *Staph. aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci

Bone and joint infections due to *Staph. aureus*

Septicemia due to *D. pneumoniae, Staph. aureus* (penicillin-sensitive and penicillin-resistant), *Pr. mirabilis, Esch. coli,* and *Klebsiella* species

Endocarditis due to *Staph. aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Kefzol™ (cefazolin sodium, Lilly).

Contraindication: KEFZOL IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

Warnings: IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics, including Kefzol, cautiously and then only when absolutely necessary. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Usage in Infants— Safety for use in prematures and infants under one month of age has not been established.

Precautions: Prolonged use of Kefzol may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When Kefzol is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false-positive reaction for glucose in the urine of patients on Kefzol has occurred with Clinitest® tablets solution.

Adverse Reactions: The following reactions have been reported:

Hypersensitivity—Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood—Neutropenia, leukopenia, thrombocythemia, and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal—Transient rise in SGOT, SGPT, BUN, and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment.

Gastro-Intestinal—Nausea, anorexia, vomiting, diarrhea, and oral candidiasis (oral thrush) have been reported.

Other—Pain at the site of injection after intramuscular administration has occurred, some with induration. Phlebitis at the site of injection has been noted.

Administration and Dosage: Kefzol may be administered intramuscularly or intravenously after reconstitution.

Dosage— In adults, usual dosage for mild gram-positive infections is 250 to 500 mg. of Kefzol every eight hours. In acute uncomplicated urinary tract infections, a dosage of 500 mg. every eight hours is usually adequate. In moderate or severe infections, the usual adult dosage is 500 mg. to 1 Gm. of Kefzol every six to eight hours. Kefzol has been administered in dosages of 6 Gm. per day in serious infections such as endocarditis. Kefzol may be used in patients with reduced renal function with the following dosage adjustments: In patients with mild to moderate impairment (creatinine clearance of 60-40 ml./min.), 60 percent of the normal daily dose given in divided doses q. 12 h. should be sufficient. In patients with moderate impairment (creatinine clearance of 40-20 ml./min.), 25 percent of the normal daily dose given in divided doses q. 12 h. should be sufficient. In patients with marked impairment (creatinine clearance of 20-5 ml./min.), 10 percent of the normal daily dose given q. 24 h. should be adequate. All dosage recommendations apply after an initial loading dose of 500 mg.

In children, a total daily dosage of 25 to 50 mg. per Kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg. per Kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of Kefzol in these patients is not recommended.

How Supplied: Ampoules Kefzol™ (cefazolin sodium, Lilly), Sterile, equivalent to 250 or 500 mg. cefazolin, 5-ml. size, rubber-stoppered; equivalent to 1 Gm. cefazolin, 10-ml. size, rubber-stoppered.

[102473]

Lilly

Additional information available to the profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

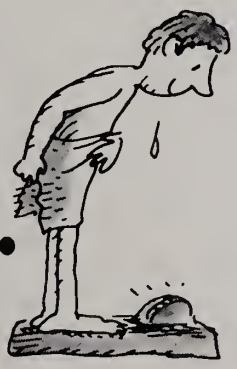
301589

Concerned about heart attack?

If you will get your husband to quit smoking...

exercise regularly...

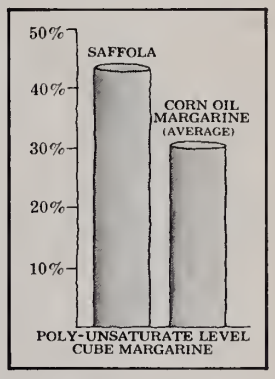
watch his weight...



and have regular checkups...

Saffola® will help lower his cholesterol.

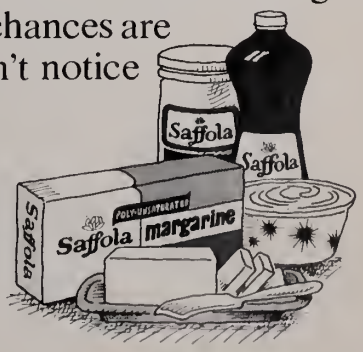
Following the doctor's orders isn't always easy. So when he recommends a low saturated fat diet, it's nice to get some help. Unlike the high-priced spread, Saffola (and, in fact, most margarines) contains no cholesterol. But that's only the beginning. Saffola Margarine is made from safflower oil — lower in saturated fats, higher in polyunsaturates than corn oil. In conjunction with a low saturated fat diet, Saffola actually helps reduce the level of blood cholesterol.



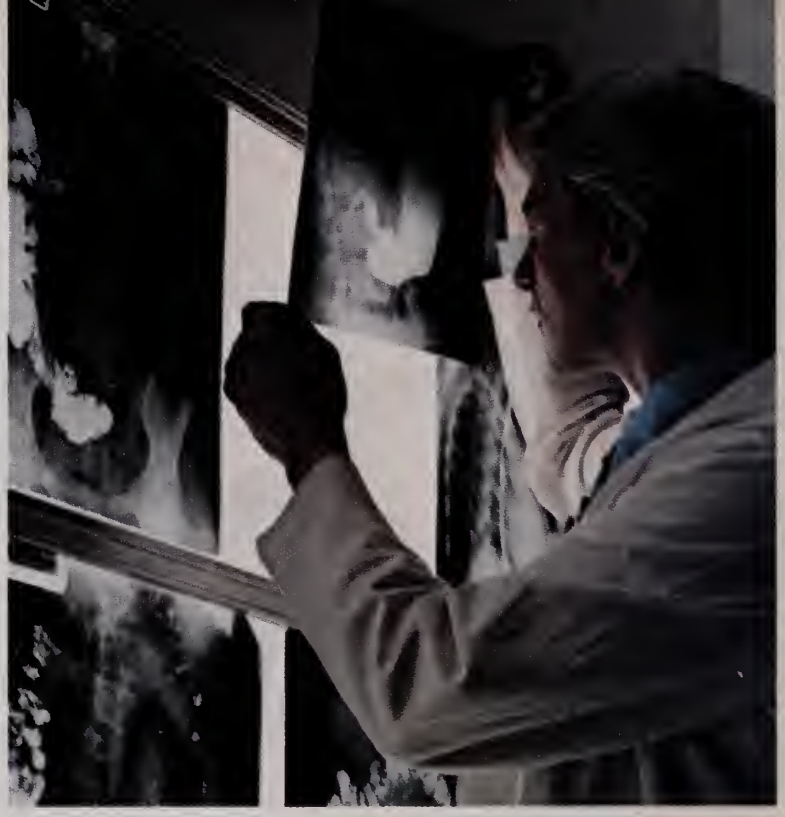
It's reassuring to know that if your doctor recommends cutting down on saturated fats, you don't have to cut down on flavor.

Saffola tastes so much like the high-priced spread, chances are your family won't notice the difference.

Saffola



When G.I. complaints occur in the absence of organic findings, underlying anxiety may be one factor



The influence of anxiety on gastrointestinal function. Excessive anxiety and tension can adversely affect the function of any portion of the gastrointestinal system. Complaints are varied, *e.g.*, epigastric pressure, heartburn, ulcer-like pain, diarrhea, etc. A vicious circle may develop in which anxiety and G.I. disorders intensify each other.

Prime objectives of total patient therapy include: symptomatic relief, removal of apprehensions about organic disease and helping the patient understand how excessive anxiety may trigger physical

---

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions

complaints. Brief counseling and the utilization of favorable factors in the patient's personality and environment can often provide needed support.

Antianxiety therapy. Antianxiety medication may prove a valuable supplement when counseling and reassurance are not sufficient to allay the patient's emotional distress and relieve his anxiety-provoked physical complaints. The agent prescribed should be both clinically effective and generally free from undesirable side effects. Librium (chlordiazepoxide HCl) meets these requirements with a high degree of consistency, and has a wide margin of safety and an excellent record of patient acceptance. The most common side effects reported have been drowsiness, ataxia and confusion, particularly in the elderly and debilitated.

Whenever anxiety is a clinically significant factor, adjunctive Librium is used concomitantly with specific gastrointestinal drugs such as anticholinergic agents. Once anxiety has been reduced to appropriate levels, treatment with Librium should be discontinued.

For relief of excessive anxiety adjunctive

Librium® 10 mg

(chlordiazepoxide HCl)

1 or 2 capsules t.i.d./q.i.d.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

---

in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Supplied: Librium® Capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Libritabs® Tablets containing 5 mg, 10 mg or 25 mg chlordiazepoxide.

The Weight of Professional Opinion

It's time for action to defend the laws and regulations that protect your patients against drug substitution.

These professional and trade organizations are united in supporting antisubstitution statutes and regulations:

The American Academy of Dermatology

The Board of Directors of the American Academy of Family Physicians

The Executive Board of the American Academy of Neurology

The Committee on Drugs of the American Academy of Pediatrics

The American College of Allergists

The Executive Committee of the American College of Obstetricians and Gynecologists

The Board of Regents of the American College of Physicians

The Board of Trustees of the American Dental Association

The Board of Trustees of the American Medical Association

The American Psychiatric Association

The Executive Committee of the National Association of Retail Druggists

The Board of Directors of the Pharmaceutical Manufacturers Association

The National Wholesale Druggists' Association

Joint Statement on Antisubstitution Laws and Regulations

The purpose of this statement is to affirm the support of the participating organizations for the laws, regulations and professional traditions which prohibit the unauthorized substitution of drug products.

Traditionally, physicians, dentists and pharmacists have worked cooperatively to serve the best interests of patients. Productive cooperation has been achieved through mutual respect as well as a common concern for the ideals of public service. This mutual respect has been reflected, in part, by joint support over the years for the adoption and enforcement of laws and regulations specifically prohibiting unauthorized substitution and encouraging joint discussion and selection of the source of supply of drug products. The basic principles of medical, dental and pharmacy practice are thus utilized and preserved in the interest of patient welfare.

The antisubstitution laws have not obstructed enhancement of the professional status of pharmacy any more than they have in and of themselves guaranteed absolute protection from unsafe drugs, or freed physicians, dentists and pharmacists from their responsibilities to patients. As a practical matter, however, such laws and regulations encourage interprofessional communications regarding drug product selection and assure each profession the opportunity to exercise fully its expertise in drug usage, to the advantage of patients.

Physicians and dentists should be urged to increase the frequency and regularity of their contacts with pharmacists in selection of quality drug products, recognizing that economies to patients can be improved through such communication, taking into account the patients' needs. The pharmacist's knowledge of the chemical characteristics of drugs, their mode of action, toxic properties and other characteristics that assist in making drug selection decisions should be utilized to the fullest extent practicable by physicians and dentists in serving their patients.

Since drug product selection entails knowledge derived from clinical experience, the physician's and dentist's roles in product selection remain primary and do not permit delegation of decisions requiring medical and dental judgments. A broader role in therapy will evolve for pharmacists as improved understanding and cooperation among the professions continue to grow.

There has been no evidence that there are convincing reasons to modify or repeal existing laws and regulations prohibiting the unauthorized substitution of another drug product for the one specified by a prescriber. It is our belief that such laws and regulations merit the joint support of the medical, dental and pharmaceutical professions and the pharmaceutical industry.

Add your opinion to the weight of other professionals and send it to your state assemblyman or legislator.

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W., Washington, D. C. 20005

MIXED ANXIETY-DEPRESSION* CUTS DEEP...

deep into the patient's family life

deep into the patient's ability to function in business

MELLARIL® (thioridazine)

TABLETS: 25 mg. thioridazine HCl, U. S. P.

A LOGICAL CHOICE FOR THE TREATMENT OF MODERATE TO SEVERE MIXED ANXIETY-DEPRESSION

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
Effective: The management of manifestations of psychotic disorders.
"Probably" effective: The relief of symptoms of neurotic depressive reaction; and control of moderate to severe agitation, hyperactivity, or aggressiveness in disturbed children.
"Possibly" effective: Alcohol withdrawal syndrome, intractable pain, psychoneuroses, senility.
Final classification of the less-than-effective indications requires further investigation.

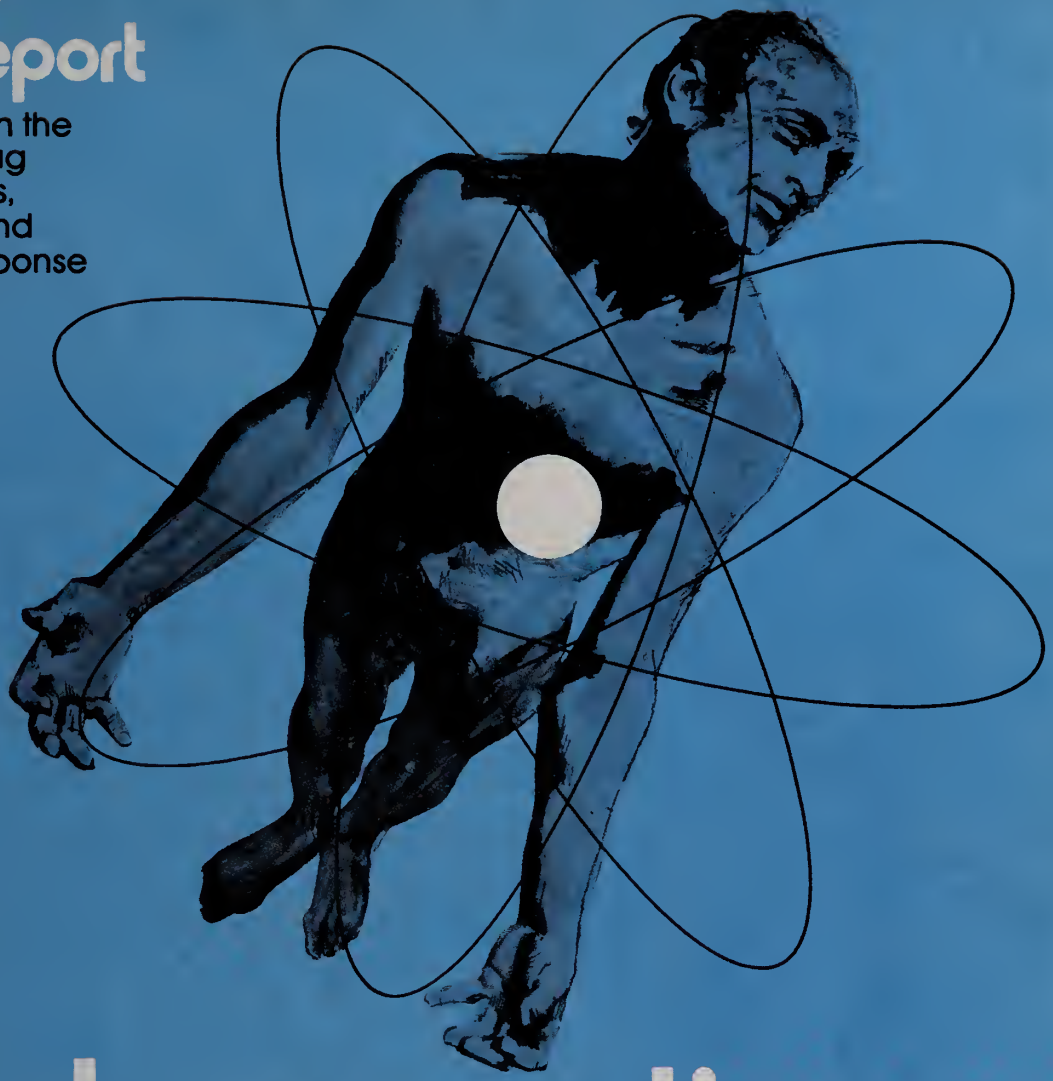
Before prescribing or administering, see Sandoz literature for full product information. The following is a brief summary.

Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree.
Warnings: Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides. During pregnancy, administer only when the potential benefits exceed the possible risks to mother and fetus.
Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy may be avoided by remaining within the recommended limits of dosage. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving), and increase dosage gradually. Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension since phenothiazines may induce a reversed epinephrine effect on occasion. Daily doses in excess of 300 mg. should be used only in severe neuropsychiatric conditions.
Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—ECG changes (see *Cardiovascular Effects* below). *Other*—A single case described as parotid swelling.
The following reactions have occurred with phenothiazines and should be considered: *Autonomic Reactions*—Miosis, obstipation, anorexia, paralytic ileus. *Cutaneous Reactions*—Erythema, exfoliative dermatitis, contact dermatitis. *Blood Dyscrasias*—Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia. *Allergic Reactions*—Fever, laryngeal edema, angioneurotic edema, asthma. *Hepatotoxicity*—Jaundice, biliary stasis. *Cardiovascular Effects*—Changes in terminal portion of electrocardiogram, including prolongation of Q-T interval, lowering and inversion of T-wave, and appearance of a wave tentatively identified as a bifid T or a U wave have been observed with phenothiazines, including Mellaril (thioridazine); these appear to be reversible and due to altered repolarization, not myocardial damage. While there is no evidence of a causal relationship between these changes and significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients showing characteristic electrocardiographic changes while taking the drug. While proposed, periodic electrocardiograms are not regarded as predictive. Hypotension, rarely resulting in cardiac arrest. *Extrapyramidal Symptoms*—Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonus, oculogyric crises, tremor, muscular rigidity, and akinesia. *Persistent Tardive Dyskinesia*—Persistent and sometimes irreversible tardive dyskinesia, characterized by rhythmical involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements) and sometimes of extremities may occur on long-term therapy or after discontinuation of therapy, the risk being greater in elderly patients on high-dose therapy, especially females; if symptoms appear, discontinue all antipsychotic agents. Syndrome may be masked if treatment is reinstituted, dosage is increased, or antipsychotic agent is switched. Fine vermicular movements of tongue may be an early sign, and syndrome may not develop if medication is stopped at that time. *Endocrine Disturbances*—Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema, false positive pregnancy tests. *Urinary Disturbances*—Retention, incontinence. *Others*—Hyperpyrexia; behavioral effects suggestive of a paradoxical reaction, including excitement, bizarre dreams, aggravation of psychoses, and toxic confusional states; following long-term treatment, a peculiar skin-eye syndrome marked by progressive pigmentation of skin or conjunctiva and/or accompanied by discoloration of exposed sclera and cornea; stellate or irregular opacities of anterior lens and cornea.

SANDOZ PHARMACEUTICALS, EAST HANOVER, N.J. 07936 73-751R SANDOZ

a new film report

dealing with the effect of drug formulations, bioassay and clinical response



biopharmaceutics

featuring...

Dr. John G. Wagner,
Professor of Pharmacy
College of Pharmacy
The University of Michigan
Ann Arbor, Michigan

Dr. Louis Lasagna,
Professor of Medicine
Professor and Chairman,
Pharmacology and Toxicology
University of Rochester,
School of Medicine and Dentistry
Rochester, New York

Dr. John L. Lach,
Associate Dean
Director of Pharmaceutical Services
College of Pharmacy
The University of Iowa
Iowa City, Iowa

Narrated by Frank Blair (Commentator with the NBC "Today" Show)

To schedule a showing of "Biopharmaceutics", fill out and return this coupon to:

"Biopharmaceutics" Film
Warner/Chilcott
201 Tabor Road
Morris Plains, New Jersey
07950

Please schedule a showing of your film, "BIOPHARMACEUTICS" for

_____ (DATE) or _____ (ALTERNATE DATE)

Name _____ Title _____

Organization _____

Address _____ (STREET) (CITY) (STATE) (ZIP)

Signature _____

MS GP-33

Must vasodilators and therapy for other diseases come into conflict?

not if the vasodilator is

VASODILAN®

(ISOXSUPRINE HCl)

the compatible vasodilator... no treatment conflicts reported

The cerebral or peripheral vascular disease patient often has coexisting disease[1] which calls for another drug along with his vasodilator. It may be a hypoglycemic, miotic, antihypertensive, diuretic, anticoagulant, corticosteroid, or coronary vasodilator.

Vasodilan is not incompatible with any of these drugs—no treatment conflict has been reported. And, unlike other vasodilators, Vasodilan has not been reported to affect carbohydrate metabolism, liver function, or intraocular pressure—or to complicate treatment of diabetes, hypertension, peptic ulcer, glaucoma, or liver disease.

In fact, there are no known contraindications to the use of Vasodilan in recommended oral doses, other than that it should not be given in the presence of frank arterial bleeding or immediately postpartum.

1. Gertler, M. M., et al.: Geriatrics *25*:134-148 (May) 1970.

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.
3. Threatened abortion.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.

Dosage and Administration: 10 to 20 mg. three or four times daily.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Adverse Reactions: On rare occasions, oral administration of the drug has been associated in time with the occurrence of severe rash. When rash appears, the drug should be discontinued. Occasional overdosage effects such as transient palpitation or dizziness are usually controlled by reducing the dose.

Supplied: Tablets, 10 mg.—bottles of 100, 1000, 5000 and Unit Dose; 20 mg.—bottles of 100, 500 and Unit Dose.

© 1973 MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA 47721 U.S.A. 734017

Mead Johnson LABORATORIES

When the asthmatic can anticipate the attack

Bronkotabs®

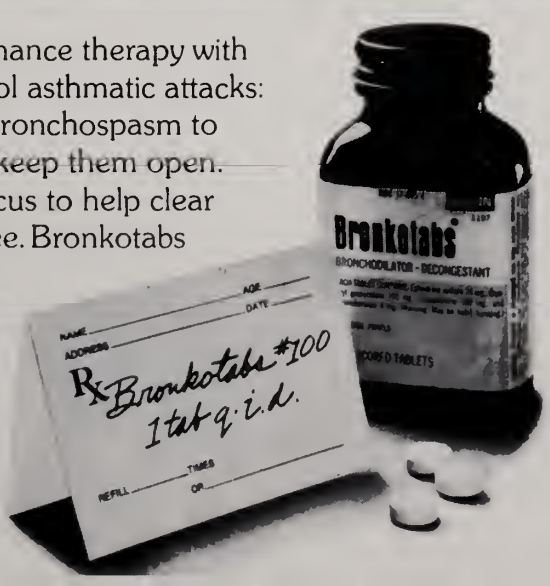
Each tablet contains ephedrine sulfate 24 mg; theophylline 100 mg; glyceryl guaiacolate 100 mg; phenobarbital 8 mg (warning: may be habit-forming).

can help forestall or relieve it

Why day to day maintenance therapy with Bronkotabs helps control asthmatic attacks:

Bronkotabs relieves bronchospasm to open airways and help keep them open.

Bronkotabs thins mucus to help clear the tracheobronchial tree. Bronkotabs decongests bronchiolar mucosa to improve the passage of air. Economical long-term therapy.



PRECAUTIONS AND ADVERSE EFFECTS: Sympathomimetic side effects are minimal, and there are none of the dangers or side effects associated with steroid therapy. However, frequent or prolonged use may cause nervousness, restlessness or sleeplessness. Should be used with caution in the presence of hypertension, heart disease or hyperthyroidism. Drowsiness may occur. Ephedrine may cause urinary retention, especially in the presence of partial obstruction, as in prostatism.

DOSAGE: Adults, one tablet every three or four hours, four or five times daily. Children over six, one-half the adult dose. Children under six, as directed.

SUPPLIED: Bottles of 100 and 1,000 tablets.

BREON

BREON LABORATORIES INC.
90 Park Avenue, New York, N.Y. 10016

Synthroid®
(sodium levothyroxine)

the smooth road to thyroid replacement therapy.

Synthroid is T4. It provides your patients with what is needed for complete thyroid replacement therapy.

Free Tab-Minder sample packages available from Flint Professional Services Department.

Indications: SYNTHROID (sodium levothyroxine) is specific replacement therapy for diminished or absent thyroid function resulting from primary or secondary atrophy of the gland, congenital defect, surgery, excessive radiation, or antithyroid drugs. Indications for SYNTHROID (sodium levothyroxine) **Tablets** include myxedema, hypothyroidism without myxedema, hypothyroidism in pregnancy, pediatric and geriatric hypothyroidism, hypopituitary hypothyroidism, simple (nontoxic) goiter, and reproductive disorders associated with hypothyroidism. SYNTHROID (sodium levothyroxine) **for injection** is indicated for intravenous use in myxedematous coma and other thyroid dysfunctions where rapid replacement of the hormone is required. The injection is also indicated for intramuscular use in cases where the oral route is suspect or contraindicated due to existing conditions or to absorption defects, and when a rapid onset of effect is not desired.

Precautions: As with other thyroid preparations, an overdosage of SYNTHROID (sodium levothyroxine) may cause diarrhea or cramps, nervousness, tremors, tachycardia, vomiting and continued weight loss. These effects may begin after four or five days or may not become apparent for one to three weeks. Patients receiving the drug should be observed closely for signs of thyrotoxicosis. If indications of overdosage appear, discontinue medication for 2-6 days, then resume at a lower dosage level. In patients with diabetes mellitus, careful observations should be made for changes in insulin or other antidiabetic drug dosage requirements. If hypothyroidism is accompanied by adrenal insufficiency, such as Addison's Disease (chronic adrenocortical insufficiency), Simmonds's Disease (panhypopituitarism) or Cushing's syndrome (hyperadrenalism), these dysfunctions must be corrected prior to and during SYNTHROID (sodium levothyroxine) administration. The drug should be administered with caution to patien with cardiovascular disease; development chest pains or other aggravations of cardiova cular disease requires a reduction in dosage.

Contraindications: Thyrotoxicosis, acute myoc dial infarction. **Side effects:** The effects of SY THROID (sodium levothyroxine) therapy are sl in being manifested. Side effects, when they occur, are secondary to increased rates of bo metabolism; sweating, heart palpitations w or without pain, leg cramps, and weight lo Diarrhea, vomiting, and nervousness have al been observed. Myxedematous patients wl heart disease have died from abrupt increas in dosage of thyroid drugs. Careful observati of the patient during the beginning of any t roid therapy will alert the physician to any t toward effects.

It has been shown that *Synthroid* (T_4) converts to T_3 at the cellular level to supply metabolic needs.[1,2]

1 *Synthroid* is T_4.

2 Because T_4 converts to T_3 at the cellular level, it provides full thyroid replacement at maintenance doses.[1,2]

3 T_4 hormone content is controlled by chemical assay.

4 *Synthroid* is assayed chemically; no biologic test is necessary to measure potency.

5 *Synthroid* provides predictable results when used with current thyroid function tests.

6 *Synthroid* is the most prescribed brand name of thyroid in the U.S. and Canada.

7 Sodium levothyroxine in *Synthroid* tablets is chemically pure. It does not contain any animal gland parts.

8 When stored properly, *Synthroid* has a longer shelf life than desiccated thyroids.

9 On a daily basis, *Synthroid* is cost competitive with other thyroid products.

The smooth road to thyroid replacement therapy.

Synthroid®
(sodium levothyroxine)

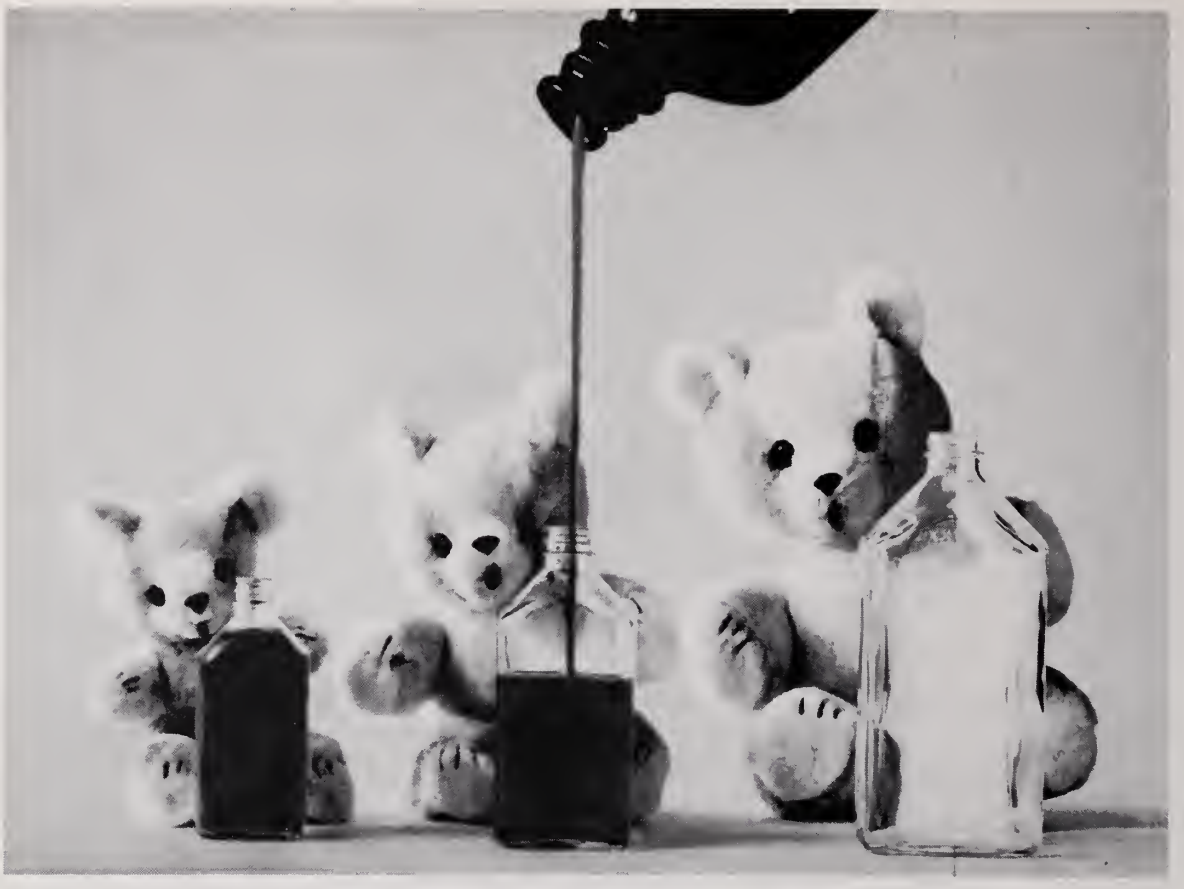
n most cases with side effects, a reduction of age followed by a more gradual adjustment ward will result in a more accurate indication he patient's dosage requirements without the earance of side effects.

sage and Administration: The activity of .1 mg. SYNTHROID (sodium levothyroxine) FILET is equivalent to approximately one grain roid, U.S.P. Administer SYNTHROID tablets a single daily dose. In hypothyroidism with- myxedema, the usual initial adult dose is mg. daily, and may be increased by 0.1 mg. ry 30 days until proper metabolic balance is ained. Clinical evaluation should be made nthly and PBI measurements about every 90 ys. Final maintenance dosage will usually nge from 0.2-0.4 mg. daily. In adult myxedema, rting dose should be 0.025 mg. daily. The dose may be increased to 0.05 mg. after two weeks and to 0.1 mg. at the end of a second two weeks. The daily dose may be further increased at two-month intervals by 0.1 mg. until the optimum maintenance dose is reached (0.1-1.0 mg. daily).

Supplied: Tablets: 0.025 mg., 0.05 mg., 0.1 mg., 0.15 mg., 0.2 mg., 0.3 mg., 0.5 mg., scored and color-coded, in bottles of 100, 500, and 1000. Injection: 500 mcg. lyophilized active ingredient and 10 mg. of Mannitol, U.S.P., in 10 ml. single-dose vial, with 5 ml. vial of Sodium Chloride Injection, U.S.P., as a diluent. SYNTHROID (sodium levothyroxine) **for injection** may be administered intravenously utilizing 200-400 mcg. of a solution containing 100 mcg. per ml. If significant improvement is not shown the following day, a repeat injection of 100-200 mcg. may be given.

1. Braverman, L. E., Ingbar, S. H., and Sterling, K.: Conversion of Thyroxine (T_4) to Triiodothyronine (T_3) in Athyreotic Human Subjects, J. Clin. Invest. 49:855-64, 1970.
2. Surks, M. I., Schadlow, A. R., and Oppenheimer, J. H.: A New Radioimmunoassay for Plasma L-Triiodothyronine: Measurements in Thyroid Disease and in Patients Maintained on Hormonal Replacement. J. Clin. Invest. *51*:3104-13, 1972.

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015



Not too little, not too much... but just right!

"Just right" amounts of Ilosone Liquid 250 can be dispensed easily from the pint bottle in *any* quantity you specify to meet your patients' precise needs—without regard to package size.

ready-mixed

ILOSONE® LIQUID 250

ERYTHROMYCIN ESTOLATE

(equivalent to 250 mg. erythromycin per 5-ml. teaspoonful)

Additional information available to the profession on request.

DISTA

Dista Products Company
Division of Eli Lilly and Company
Indianapolis, Indiana 46206

400054

Refer to: Coulson AS, Lucas ZJ, Condy M, et al: Forty-day fever —An epidemic of cytomegalovirus disease in a renal transplant population. West J Med 120:1-7, Jan 1974

THE WESTERN
Journal of Medicine

FORTY-DAY FEVER

An Epidemic of Cytomegalovirus Disease in a Renal Transplant Population

ALAN S. COULSON, MA, MB, PhD, ZOLTAN J. LUCAS, MD, MERCY CONDY, RN, *and* ROY COHN, MD, *Stanford*

An epidemic of cytomegalovirus disease (CMV) occurred in 38 percent of 34 renal transplant recipients during an 18-month period. A characteristic clinical pattern was noted: 40 days following transplantation, daily fevers recurred for periods of four to six weeks. This fever in conjunction with a diffuse interstitial pneumonitis and impaired hepatic and renal function constituted a diagnostic tetrad. Of all the laboratory techniques, throat and urine cultures were the most consistent in confirming the diagnosis.

Analysis of the epidemic implicated the communal hemodialysis unit as the source of exposure to the virus. CMV was not seen in the first 86 patients who received transplants in the program, but with increasing use of hemodialysis, the percentage of patients with positive serologic reaction for CMV increased dramatically.

A DISTURBING CONSEQUENCE of immunosuppressive therapy is the appearance of opportunistic infection in the compromised hosts. As early as 1964 cytomegalovirus (CMV) was recognized as a contributory cause of the pneumonic disease observed in 47 percent of a group of 32 organ transplant recipients who died after immunosuppressive therapy. In four of these cases CMV was the only agent detected in the lungs.[1] Kanich and Craighead[2] thought that CMV disease had contributed to the death of two renal transpant recipients, and possibly a third, in a series of 25 autopsies; in addition CMV disease of uncertain pathologic significance was noted in five more patients. In the series described by Fine et al,[3] eight out of 21 pediatric recipients had cytomegaloviruria, four of these were clinically ill, one patient dying of CMV pneumonitis.

One important consideration in comparing the

From the Department of Surgery, Stanford University School of Medicine.

Submitted, revised, April 18, 1973.

Dr. Coulson is a Leverhulme Research Fellow and the recipient of the British Medical Association Ernest Hart Award and the University of London Laura di Saliceto Studentship.

This study was supported in part by the General Clinical Research Center's Branch, N.I.H., Grant RR-70.

Reprint requests to: A. S. Coulson, MB, PhD, Department of Surgery, Stanford University School of Medicine, Stanford CA 94305.

incidence of clinical infections at different institutions is that human CMV is not antigenically homogeneous.[4] Medearis[5] has described as many as 14 strains. It is possible that variations in severity of clinical disease may be due to strain differences in virulence. Hitherto a strain of epidemic virulence has not been described. The justification for thinking of the outbreak we experienced as an epidemic rests on the fact that although only one possible case of CMV disease was encountered in our initial 86 transplants, 13 cases occurred in the next 34 consecutive recipients (38 percent). The immunosuppressive protocol had not been altered. All patients were ill with a clinically unique syndrome, manifested by the occurrence of fever 40 days after transplant, persistence of fever for four to six weeks, the development of interstitial pneumonitis, and varying degrees of hepatic and renal involvement. This paper describes the clinical features and the associated laboratory studies.

Materials and Methods

At Stanford University Hospital between 1 April 1970 and 30 September 1971, 34 patients had renal allografts transplanted that functioned for at least one month. The patients were nursed in the hemodialysis unit before transplantation, and in the intensive care unit and on two contiguous nursing floors following transplantation. The nursing staff moved freely within each of these areas, but not commonly between the areas. The renal transplant team was in close contact with the patients in all three areas. The hemodialysis unit consists of a five-bed room occupying 780 square feet. Close atmospheric contiguity exists between patients, and dispersion of airborne particles could occur readily. An epidemic outbreak of Australia antigen hepatitis in this setting has been described.[6] The rooms on the nursing floors were either two-bed rooms or six-bed wards. In the past, renal transplant recipients were commonly roomed together.

The diagnosis of CMV infection was suggested when a patient began to have recurrent fever over 38.7°C 40 days after his transplant, which was accompanied by a diffuse interstitial pneumonitis and by hepatic and renal impairment. Laboratory confirmation of the infection was necessarily retrospective and was provided by virus culture of throat washings, blood or urine. The cultures were set up in the conventional manner by adding 0.2 ml of the appropriate material to culture tubes containing human fibroblasts. The cultures were

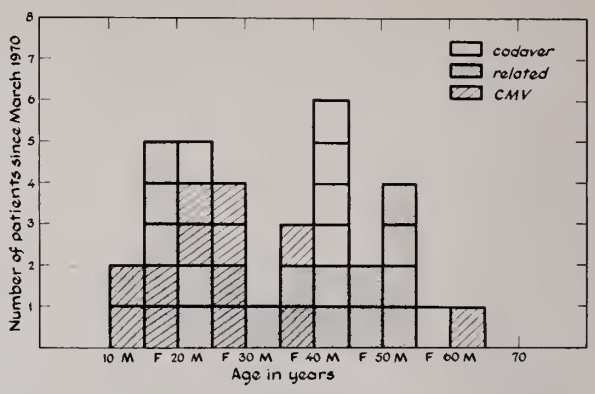


Chart 1.—Incidence of CMV disease in all recipients transplanted during the epidemic in relation to age, sex or type of renal donor.

examined twice weekly for a month for a cytopathic effect. Anti-CMV antibody titers were determined by a standard complement fixation technique. A standard serum was used to titrate a cytomegalovirus complement fixing antigen (Flow Laboratories) and the latter was then compared with a series of dilutions of the patient's serum. The mixtures were incubated 18 hours at 4°C with guinea pig complement, following which a 2 percent suspension of sensitized sheep red cells was added.

Autopsy or biopsy slides to be examined for evidence of CMV were prepared and stained in the routine manner with hematoxylin and eosin. Evidence of CMV infection was provided by finding cells with large intranuclear eosinophilic inclusion bodies with a peripheral halo. For the cytological examination of urine, the urine was filtered through nucleopore filters (General Electric Company, Pleasanton, California) and stained with Papanicolaou stain to demonstrate either actual inclusion bodies or other nuclear changes consistent with CMV infection.

Results

Clinical Syndrome of Disseminated CMV Disease

A histogram of age and sex of the 34 recipients is illustrated in Chart 1. It parallels the age distribution of the 86 patients who had transplants before the epidemic. CMV disease appeared mainly in patients under 40 years of age: Twelve of 20 patients under 40, but only one of 14 above 40, were afflicted.

The patients who were victims of the current CMV epidemic presented with a virtually diagnostic symptom complex. The first clinical sign was a rise in temperature, which ran as high as 41°C.

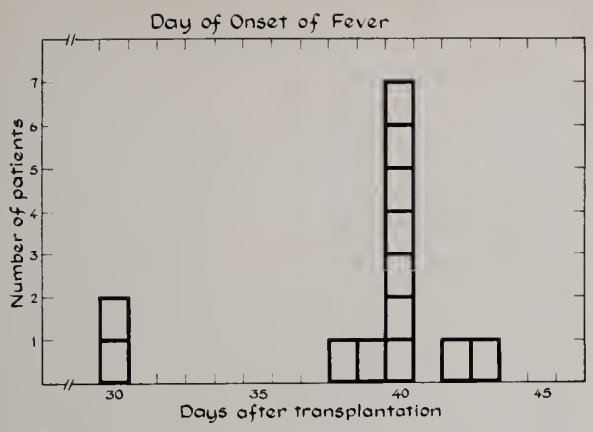


Chart 2.—The time of onset of clinical CMV disease following transplantation.

Figure 1.—Patient LR64, x-ray film of chest at the height of pneumonitis, showing dense bilateral nonspecific interstitial infiltrates.

The febrile episodes recurred daily, and were not sustained. Nasopharyngeal and conjunctival irritation, and non-productive cough were very early symptoms. Most striking was the fact that the onset of fever and symptoms commonly occurred 40 days post-transplant (Chart 2). These features and the subsequent occurrence of dyspnea which heralded generalized pulmonary infiltrates, in conjunction with renal and hepatic dysfunction and the fever, made up a diagnostic tetrad. The clinical picture was complicated to a greater or lesser degree by involvement of other organ systems (Table 1).

This clinical syndrome was not recognized in the 85 patients with transplants performed from 1964 to April 1969. Retrospective analysis of the hospital charts and the transplant registry flow sheets did not show a pattern of "40-day fever." Postmortem examination of 22 transplant failures showed cytomegalic cells in the lungs in only one patient. One other patient became icteric two years after transplantation (bilirubin, 4 mg per 100 ml) and had cytomegalic cells noted in a liver biopsy. She did not, however, have other organ involvement. The syndrome was first recognized in April 1970, and from then to September 1971 there was always a recipient with clinical CMV in the hospital.

Pneumonitis. Breathlessness and elevated respiratory rate occurred in all the affected patients. Roentgenograms taken at this stage generally showed bilateral, nonspecific interstitial infiltrates, spreading from the hilar zones (Figure 1). In addition, blood gases showed a decidedly lowered pO_2 (40 to 72 mm). Exercise tolerance was considerably diminished. Respiratory failure was the final common pathway for the five patients who died, superinfection with pathogenic organisms leading to overwhelming pneumonia.

Renal. All patients had clinical evidence of decreased renal function during the febrile illness. The creatinine clearance decreased to one-third to one-half of the previous stable level. Renal biopsies demonstrated inclusion bodies in two, urine cytology showed cytomegalic epithelial cells in two, and the other nine had CMV cultured from the urine. Biopsies in eight patients during the febrile episode indicated rejection to be significant in the reduction of renal function in only one. The strongest clinical indication that the decreased renal function was due to CMV nephritis was the finding that renal function improved with a *lowering* of immunosuppression in 11 of the 13 patients.

Hepatic. Evidence for CMV hepatitis rested mainly on the derangement of chemical liver function tests which occurred insidiously in the second or third week of the fever and were detected by virtue of daily laboratory tests. No clear-cut correlation could be seen between the onset of hepatic involvement and specific clinical findings except for the reduced serum albumin concentrations which probably contributed to the hypotension many of the patients experienced. During the phase of hepatic involvement the patients were not jaundiced and did not complain of any hepatic pain or tenderness. Hepatomegaly was not detectable clinically. Elevation in the SGOT to 100 to 200 units occurred in nine of the 13 patients during the fever, this rise probably being more significant than in other classes of patients in view of the finding that hemodialysed patients commonly have very low SGOT levels.[7]

A typical example was a patient LR81 (see Table 1) whose liver function tests became ab-

TABLE 1.—*Systemic Involvement in CMV Disease*

Patient	*Age/Sex*	*Fever*	*Nephritis*	*Hepatitis*	*Pneumonitis*	*Neurologic*	*Hemopoietic*	*Other Associated Disease*†
LR64*	19♂	+	+	+Bx‡	+	−	↓WBC	−
LR69	20♀	+	+Bx	+Bx	+	"Blackout"; Catatonia	↓WBC	−
C12b	34♀	+	+	−	+	.....	↓WBC	−
C12a	63♂	+	±Autopsy	+	+Autopsy	.....	−	Tuberculosis, left upper lobe, active; CMV pneumonitis, extensive
LR74	21♀	+	±	+Autopsy	+Autopsy	Encephalitis	↓WBC ↓Platelets	CMV pneumonitis, extensive; Gram negative bronchopneumonia; Severe thrombocytopenia
LR75	25♀	+	±Culture§	+	+Autopsy	Encephalitis	↓WBC ↓Platelets	CMV pneumonitis, extensive; Systemic Candidiasis; Pseudomonas pneumonitis; AuAg+ hepatitis
LR76	13♂	+	+	−	−	Headaches	−	−
LR81	34♀	+	±Culture	+Bx	+	.....	−	−
C15b	22♀	+	+	+	+	Uveitis; Headaches; Encephalitis	↓WBC ↓Platelets	Pulmonary emboli with secondary cor pulmonale; Aspergillus, pulmonary, with necrosis; CMV pneumonitis, bilateral
LR82	23♂	+	?Recurrent glomerulo-nephritis	+	+	.....	−	−
C18a	21♂	+	+	−	+	.....	↓WBC	−
C18b	33♀	+	ATN¶ Rejection	+	+	Encephalitis; Inclusion bodies in brain	↓WBC ↓Platelets	CMV pneumonitis, extensive; Pseudomonas septicemia
LR87	13♀	+	+	+	+	.....	↓WBC	−

*Code symbol *LR* refers to a living related donor; *C* refers to a cadaveric donor; letters *a* and *b* refer to the two kidneys transplanted from a single cadaveric donor. This system is uniformly followed in our previous publications about clinical results in this group of patients.
†As demonstrated at postmortem examination.
‡Cytomegalic inclusion disease diagnosed by biopsy.
§Cytomegalovirus isolated by culture from biopsy tissue.
¶Acute tubular necrosis.

normal in the second week of fever (bilirubin 1-2 mg per 100 ml, SGOT 225 units, LDH 430 units and albumen 2.8 grams per 100 ml), and a percutaneous liver biopsy at this time showed CMV inclusion bodies. In the case of patient LR69 deterioration in function was detected in the third week of fever (SGOT 220 units, albumen 1.5 grams per 100 ml), and a biopsy at this time showed diagnostic inclusion bodies with portal fibrosis and inflammation. Laboratory data in the third week of fever of patient C12a included an LDH of 375 units, SGOT 90 units and albumin 1.5 grams per 100 ml) but in this case the liver biopsy was nondiagnostic. In a fourth patient, CMV was cultured from liver biopsy material.

One patient (aged 13) had an elevation of alkaline phosphatase to 340 along with LDH of 345 and SGOT of 150 units. This increased alkaline phosphatase in young patients has previously been noted by Sobel and Fanaroff.[8]

In all cases, on defervescence the liver function tests returned to normal, and there appeared to be no residual damage.

Cardiovascular. Hypotension was a relatively frequent finding in patients during the course of CMV infection. Many contributing causes are responsible: decreased synthesis of albumin accompanying CMV hepatitis; anorexia associated with high fevers; and possibly CMV myocarditis and decreased cardiac output. In support of the latter possibility is the occurrence of various arrhythmias during the course of the CMV fever in patients with no previous history of cardiac disease.

Gastrointestinal. Heartburn was noted by a number of patients and was usually relieved by taking milk and magnesium-aluminum hydroxide. Although gastrointestinal bleeding developed in four patients, this may have been due to other concurrent predisposing causes (low platelet counts, prednisone, or systemic candidiasis).

Neurologic. Four of the five patients who died showed histologic changes characteristic of viral encephalitis, and two of these had demonstrable nuclear inclusion bodies. A detailed presentation of the neuropathologic findings has been published.[9] Clinical symptoms of encephalitis were vague, with no focal or lateralizing neurologic signs. One patient (LR74) with established CMV encephalitis exhibited paranoid ideation and perseveration, with intermittent disorientation. She had alternating postural tremor in all limbs, tongue and mouth during voluntary movement, which disappeared at rest. She also had muscle wasting and diffuse motor weakness. The cerebrospinal fluid contained 24 mg protein and 72 mg glucose per 100 ml, but no cells. A brain scan was unremarkable and an electroencephalogram showed generalized slowing of the dominant rhythm. Another patient (C186) with CMV encephalitis became psychotic and in addition had dysphagia and parasthesias in hands and thighs. In her case also loss of muscle bulk was associated with generalized weakness. The cerebrospinal fluid contained 2 mononuclear cells per cu mm, and the protein content was 44 mg and glucose 87 mg per 100 ml.

A third patient (LR69) showed pronounced weakness at the height of her disease and lapsed into a catatonic state for four days, refusing to talk or eat. Other neurologic studies on this patient were unremarkable. A fourth patient (C156) had slurring of speech and nystagmus just before she died. An EEG at this time was interpreted as consistent with toxic encephalitis; the CSF was unremarkable except for an opening pressure of 220 mm of water. Blurred vision also developed, probably related to the CMV uveitis found at autopsy.

In general, neurologic diagnostic procedures including scans and arteriograms were of very little help in diagnosing CMV encephalitis. Cultures of spinal fluid were negative on three occasions in patients with viruria. On no occasion was pleocytosis found.

Hemopoietic system. Leukopenia developed in more than half the patients (leukocytes below 2,500 per cu mm) during the febrile period. Azathioprine therapy alone could have accounted for this complication, and a combination of azathioprine therapy and CMV infection may have acted synergistically to depress the bone marrow. Granulocyte counts generally returned to normal levels in four to eight days, following reduction in azathioprine dosage. Atypical lymphocytes in smears of peripheral blood were detected in three of the 13 patients.

Effectiveness of the Diagnostic Methods

The means by which laboratory tests confirmed the clinical diagnosis are indicated in Table 2. The yield of postive results from culture of throat washings, buffy coat of blood, urine and biopsy material, as well as from cytologic study, is also indicated. With one exception (Case C18a), culture of urine and throat washings provided the most consistent method of confirmation. Culture

TABLE 2.—*Laboratory Confirmation of Clinical Diagnosis—Yield of Positive Results from Various Laboratory Tests*

Patient	Confirmatory Laboratory Tests	Culture of Throat	Culture of Urine	Culture of Blood	Culture of Biopsy	Urine Cytology	Renal Biopsy	Liver Biopsy	Reciprocal of Anti-body titer
LR64	Inclusion bodies in liver biopsy	nd	2/4	nd	nd	0/3	0/1	1/1	128
LR69	Inclusion bodies in liver biopsy	nd	0/1	nd	nd	nd	1/1	1/1	64
C12b	+culture urine	nd	7/7	0/1	nd	0/1	0/2	nd	256
C12a	Autopsy: Inclusion bodies kidney and lung	nd	nd	nd	nd	0/2	0/1	0/1	64
LR74	+blood culture +culture liver, lung (autopsy)	nd	0/2	2/3	nd	nd	0/1	nd	64
LR75	+culture in urine, throat washings	2/3	5/7	0/1	nd	nd	nd	nd	64
LR76	+culture in urine, throat washings	1/3	2/7	0/3	nd	0/2	nd	nd	128
LR81	+culture in blood, throat and liver biopsy. Inclusion bodies in liver biopsy	2/4	1/2	0/2	1/1	0/1	nd	1/1	1024
C15b	+culture throat washings, urine	3/4	4/8	0/2	nd	0/4	0/1	nd	256
LR82	+culture throat washings, urine	2/3	2/2	0/2	nd	nd	nd	nd	256
C18a	+inclusion bodies urine cytology	0/5	0/4	0/4	nd	2/3	nd	nd	256
C18b	+culture urine, throat washings	1/1	1/1	nd	nd	0/3	0/1	nd	64
LR87	+culture throat washings, urine; Inclusion bodies	2/4	2/5	0/3	nd	3/10	0/2	nd	64

TABLE 3.—*Incidence of Clinical CMV Infection and Anti-CMV Antibodies in Relation to the Time Hemodialysis Was Begun*

	I Pre-Hemodialysis 1964-1968 Total Patients=21		II Early Hemodialysis 1968-1969 Total Patients=20		III Current Hemodialysis 1969-1971 Total Patients=34	
	Number of Patients	Percent of Total	Number of Patients	Percent of Total	Number of Patients	Percent of Total
CMV Antibody Titer Greater than 1:16	7	33	15	75	29	85
Clinical Disease	1	4	0	0	13	38

of blood for virus or cytologic examination of the urine was quite often negative when throat or urine cultures were positive for CMV. Similarly, examination of renal biopsies for inclusion bodies often yielded negative results although viruria was present. The CMV antibody titers after the onset of the illness are also shown in Table 2. Before transplant, seven patients had positive titers (greater than 1:16), and six had negative titers. After transplant titers in all cases rose to greater than 1:64, some as high as 1:1024 and 1:2048. However, similar increases were found in CMV antibody titers in patients who had transplants during this period and did not have clinical disease. For this reason, great significance could not be attached to a rising titer alone.

The time at which specimens were obtained during the 30 to 40 day febrile period did not seem to influence the likelihood of obtaining positive cultures.

Possible Causes of the CMV Epidemic

Transplant recipients had constant exposure to the renal transplant team and the hemodialysis unit. Serologic titers for anti-CMV were negative in all the members of the transplant team. Three of the 15 dialysis staff tested (total staff, 26) had positive reaction in low titers (1:16). In attempting to analyze the possible role of the hemodialysis unit as a reservoir of infection, the incidence of CMV infection and CMV disease in relation to the type of dialysis was tabulated (Table 3). Of the 135 patients who had transplant operations, the first 51 received peritoneal dialysis. Twenty-one long-term survivors were available for serologic testing in late 1971, and 33 percent of them had detectable anti-CMV titers. Thirty-five recipients were hemodialyzed before the first case of CMV disease occurred, and 20 of these were available for testing. Retrospectively, 75 percent of this group of 20 showed serologic evidence of infection (titers greater than 1:16), but there was no clinical disease. Finally, 34 patients were prepared by hemodialysis in the period of the epidemic, and 94 percent of them have become serologically positive. Forty-two percent of this group showed clinical disease.

Random checks for anti-CMV antibody titers in the non-transplant patients who have been hemodialyzed since April 1969 were carried out on

stored frozen sera used in an unrelated study. These showed that 50 to 73 percent of the dialyzed population at any one time had anti-CMV titers greater than 1:16. Only two of twelve patients who were dialyzed in the unit for longer than six months remained serologically negative.

Discussion

Cytomegalovirus infection is one of the numerous possible infective complications of immunosuppression. This paper describes an epidemic of CMV which lasted 18 months in our renal transplant population and which was marked by its virulence. During this time five of the thirteen afflicted patients died. Those who survived had a stormy postoperative course with a high morbidity.

Of all the aspects of CMV infection in the outbreak, interstitial pneumonitis was the most feared complication, not only because of its direct effect in decreasing oxygenation, but also because it predisposes the patient to superinfection with pathogenic organisms. CMV infections have been described previously in immunosuppressed patients,[4] but the degree of virulence we encountered and the constancy of the early clinical manifestations were unusual. The strikingly regular onset of fever 40 days after transplantation, and the serologic conversion between the eighth and twelfth weeks in all patients transplanted suggests a common source of exposure.

There are several circumstantial lines of evidence to implicate the dialysis unit as the source of exposure to CMV:

1. Since the epidemic, 50 to 70 percent of the patients being dialyzed on the unit at any one time have high serologic titers. There are abundant studies showing that asymptomatic CMV carriers may have high titers of complement fixation antibody and excrete virus in the urine or throat secretions.

2. Eighty-five percent of patients on chronic dialysis for more than six months developed high titers of complement fixation antibody. These patients were not exposed to the transplant team in any regular fashion.

3. The physical design of the dialysis unit with close proximity of patients to one another provides an environment in which airborne particles could be rapidly disseminated to all occupants. Dialyzed patients routinely are exposed to this environment for 24 to 36 hours a week.

4. This unit has already experienced an epidemic of Australia antigen-associated hepatitis[6] which was not controlled until Australia antigen-positive patients were dialyzed in an isolation room separate from the dialysis facilities for Australia antigen-negative patients. The factors which made the dialysis unit a likely repository for hepatitis—frequent dispersion of blood droplets or other body secretions into the environment in which individuals could not adequately be isolated from one another—would similarly apply to CMV dissemination.

We would like to suggest that a latent form of infection stemming from a common source is established in the dialysis patients, and that because of faulty cellular or humoral immune mechanisms existing in uremic patients, it persists in a fashion readily activated by immunosuppression. Infection may occur as a result of aspiration of airborne droplets from secretions, but transfer by blood transfusions has not been excluded. The immune factors permitting the establishment, persistence and activation of latent intracellular infections caused by the herpescytomegalo group of viruses is poorly understood.

In a population of patients already prey to numerous complications, we have documented another, a virulent form of CMV whose hallmark is a particularly debilitating and injurious pneumonitis. Evidence has been presented to suggest that the infection may be acquired initially in the hemodialysis phase of the patient's course, and that the full devastating impact of the disease is then seen during the subsequent transplant phase.

REFERENCES

1. Hill RB, Rowlands DT, Rifkind D: Infectious pulmonary disease in patients receiving immunosuppressive therapy for organ transplantation. N Engl J Med 271:1021-1027, 1964

2. Kanich RE, Craighead JE: Cytomegalovirus infection and cytomegalic inclusion disease in renal homotransplant recipients. Am J Med 40:874-882, 1966

3. Fine RN, Crushkin CM, Anand S, et al: Cytomegalovirus in children postrenal transplantation. Am J Dis Child 120:197-202, 1970

4. Krech VH, Jung M, Jung F: Cytomegalovirus Infections of Man, New York, Karger, 1971

5. Medearis DN: Observations concerning human cytomegalovirus infection and disease. Bull Hopkins Hosp 114:181-211, 1964

6. Reed W, Lucas ZJ, Kempson R, et al: Renal transplantation in patients with Australia antigenemia. Transplantation Proc 3: 343-345, 1971

7. Wolf PL, Williams D, Coplon N, et al: Low aspartate transaminase activity in serum of patients undergoing chronic hemodialysis, Clin Chem 18:567-568, 1972

8. Sobel JD, Fanaroff AA: Cytomegalovirus infection with raised alkaline phosphatase. Lancet 2:689, 1968

9. Dorfman LJ: Cytomegalovirus encephalitis in adults. Neurology 23:136-144, 1973

Refer to: Gottlieb LS, Boylen TC: Pulmonary complications of drug abuse. West J Med 120:8-16, Jan 1974

Pulmonary Complications of Drug Abuse

LEON S. GOTTLIEB, MD, *and* THOMAS C. BOYLEN, MD, *Los Angeles*

Complications resulting from drug abuse more frequently affect the lung than any other organ. The spectrum of pulmonary complications associated with drug abuse is wide. The current practice of using mixtures of drugs is mainly responsible for the increase in pulmonary complications. The chief complications observed in a series of 241 drug abuse patients were aspiration pneumonitis (12.9 percent), pulmonary edema (10.0 percent), and pneumonia (7.5 percent).

DRUG ABUSE frequently results in pulmonary complications of well defined categories. The heroin addict should be considered as part of multiple drug abuse. The drug the patient abuses may contain varying amounts of different active drugs as well as toxic adulterants.[1] The pattern of drug abuse keeps changing as the list of drugs associated with drug abuse constantly expands.[2] The more common drugs observed in the series herein reported includes the congeners of heroin, barbiturates, amphetamines, cocaine, cannabis, and ethanol. Adverse reactions also occur from a loss of opiate tolerance, nonuniformity in drug potency, effect of potentiating drug mixtures, contaminants, and infections due to nonsterile injections.

At the Los Angeles County-University of Southern California Medical Center, there were 264 admissions for heroin-related drug abuse during the period 1971-1972. 241 patients were admitted for pulmonary complications; 23 patients were admitted for heroin drug withdrawal or nonpulmonary complications. The pulmonary complications consisted of clearly defined entities and are

TABLE 1.—*Pulmonary Complications Associated with Drug Abuse (241 Patients)*

	Number of Patients	*Percent*
Overdose, coma, and respiratory depression	137	56.8
Pulmonary edema	24	10.0
Pneumonia	18	7.5
Aspiration pneumonitis	31	12.9
Atelectasis	6	2.5
Septic pulmonary emboli	11	4.6
Lung abscess	12	5.0
Pulmonary fibrosis: Pulmonary vascular talc granulomatosis	2	.8

From the Los Angeles County-University of Southern California Medical Center, Los Angeles.

Submitted July 2, 1973.

Reprint requests to: L. S. Gottlieb, MD, Room 11-900, LAC-USC Medical Center, 1200 N. State St., Los Angeles, CA 90033.

Figure 1.—(Case 1) Pulmonary edema (diffuse and confluent alveolar infiltrates).

Figure 2.—(Case 1) Chest film showing complete clearing of pulmonary edema.

listed in Table 1. Illustrative cases will describe these complications.

Overdose, coma, and respiratory depression

Patients admitted for drug overdose, coma, and respiratory depression were usually in stage 1 or stage 2 coma and retained good cough and gag reflexes. These patients were given oxygen by Ventimask® (35 percent). Arterial blood specimens were immediately collected for determinations of blood gases, for narcotic and non-narcotic screens, and for glucose and creatinine determinations. Patients with weak or absent gag and cough reflexes were intubated and gastric lavage was instituted. Mechanical ventilation was administered until the blood gases were at a safe level. Urine specimens were obtained for narcotic and non-narcotic screens and routine urinalysis. A chest x-ray film was routinely taken. The majority of these patients responded within 24 hours and were discharged.

Pulmonary edema

Pulmonary edema is one of the critical complications of heroin overdose and may result in sudden death or necessity for admission to hospital. A white or pink froth is frequently found in the mouth or nose; respiratory depression, cyanosis, and constricted pupils are usually evident. Moist rales, rhonchi and wheezes may be heard over the chest. The systolic blood pressure is variable, but is seldom below 90 mm of mercury. Needle tracks should be searched for, and occasionally they are found in bizarre locations.

Case 1.—A 24-year-old man was admitted to the emergency room comatose and cyanotic, with a bloody froth coming from his mouth. The patient had been drinking ethanol and had taken a "fix" of heroin intravenously just before lapsing into unconsciousness. He had also been a regular marijuana smoker and had taken amphetamines at various times. Blood pressure was 100/70 mm of mercury and body temperature 96°F. Pin point pupils were present; gag and cough reflexes were absent. Moist rales and rhonchi were heard over his chest. The arterial blood gases (room air) were pO_2 26 mm Hg, pCO_2 47 mm Hg, pH 7.25, HCO_3 18 mEq/L. Narcotics and related bases were detected in a urine sample. The chest x-ray film showed diffuse and confluent alveolar infiltrates (Figure 1).

The patient was intubated and attached to a ventilator with an oxygen concentration of 100 percent. Naloxone (Narcan®) 0.4 mg and furosemide (Lasix®) 40 mg were administered intra-

Figure 3.—(Case 2) Pneumonic consolidation in the left lung.

Figure 4.—(Case 3) Aspiration pneumonitis of right lower lobe.

venously. Steroids were given for 48 hours. An x-ray film of the chest five days later showed complete clearing of the pulmonary edema (Figure 2).

Pneumonia

Pneumonia associated with drug abuse may be due to direct bacterial invasion or may follow pulmonary edema or a pulmonary infarct.

Case 2.—An 18-year-old comatose patient was admitted to the emergency room. He had been found at a party with heroin needles, barbiturate tablets, and amphetamines in his pockets. Reflexes were absent, the pupils were constricted, and there were multiple needle scratches over the extremities. The blood pressure was 100/60 mm of mercury, the pulse rate 100 and the respiratory rate 20. Diffuse rhonchi were heard over the left side of the chest. Sputum culture showed numerous Pneumococci and Klebsiella organisms. Leukocytes numbered 20,000 per cu mm. A culture of blood was negative. A blood specimen showed the presence of long-acting barbiturates, 17 mg per 100 ml, and a urine specimen was positive for narcotic bases. The arterial blood gases (room air) were pO_2 34 and pCO_2 49 mm of mercury, pH 7.26 and T_{40} 22. An x-ray film showed a pneumonic consolidation of the left lung (Figure 3). The patient was intubated and attached to a ventilator. Nalorphine (Nalline®) 10 mg was given intravenously. Cephalothin and kanamycin were given every six hours. The patient recovered and was discharged two weeks after admission.

Aspiration pneumonitis

Vomiting and aspiration of gastric contents into the lungs are often associated with drug overdose. Milk is frequently found in the aspirated material. Milk is sometimes given orally or intravenously by heroin users in the mistaken belief it is a resuscitative procedure. The increasing hypoxemia that follows aspiration is indicative of aspiration pneumonitis.

Case 3.—A 19-year-old man was admitted to the emergency room in a semicomatose state. He was a known chronic heroin and barbiturate user and, while being transported to the hospital he had aspirated vomitus.

On admission to the ward, the patient was awake and complained of pain in the right side of the chest. He had fever and a rapid pulse. Short-acting barbiturates, 1.8 mg per 100 ml were found in the blood and narcotic bases were detected in the urine. A chest x-ray film showed a patchy infiltrate extending from the hilum to the right lower lobe (Figure 4). Bronchoscopic exam-

Figure 5.—(Case 4) Chest film showing atelectasis of left lung.

Figure 6.—(Case 5) Chest film showing a round infiltrate in the right costophrenic sulcus with an area of discoid atelectasis proximal to it, consistent with a pulmonary infarct.

ination with lavage was carried out. The right main bronchus was inflamed and moderately edematous. Discolored mucoid material obtained from the bronchus had a pH of 5. A broad spectrum antibiotic and steroids were administered for 72 hours. X-ray studies showed complete resolution of the pulmonary density after five days.

Atelectasis

Atelectasis frequently follows drug overdose. The degree of collapse is variable, ranging from segmental to total involvement of one lung. Atelectasis may result from the retention of secretions due to an ineffectual cough reflex, or may follow the aspiration of gastric contents into the tracheobronchial tree. When atelectasis follows the aspiration of gastric contents, the right lower lobe is usually involved. The posterior segments of the upper lobes and the superior basal segments of the lower lobes are prone to atelectasis due to the gravitational spread of secretions into the dependent areas of the lung.

Case 4.—An 18-year-old man, a heroin addict, was admitted to the emergency room in a comatose state. He was cyanotic and respiration was depressed. The blood showed long-acting barbiturates, 15 mg per 100 ml, and narcotic bases were detected in the urine. The left hemithorax was dull on percussion, and rhonchi and wheezes were heard over the entire area. A chest x-ray film showed opacification of the left lung with the heart shadow and mediastinum shifted to the left hemithorax (Figure 5). At bronchoscopy, a large viscid mucous plug was suctioned from the left main bronchus. The left lung subsequently re-expanded.

Septic pulmonary emboli

Septic pulmonary emboli associated with drug abuse have their origin from an infected subcutaneous, intramuscular, or intravenous injection site. An alternate source for emboli is tricuspid endocarditis. The embolic material from the injection site and that from right heart endocarditis or tricuspid valvulitis is usually bacterial.

Case 5.—(Septic pulmonary embolus from a peripheral site.) A 26-year-old woman, a known heroin addict, was admitted to the ward as a transfer from another hospital. On admission, numerous infected needle tracks were noted over both antecubital areas and legs. The temperature was elevated, the pulse was 110, the blood pressure 144/60 mm of mercury. No abnormalities were noted on auscultation of the heart. Coarse rales were present over the right lower hemithorax. The leukocyte count was 24,200 per cu mm. A

Figure 7.—(Case 6) Patchy infiltrates in both bases, with central lucencies suggestive of cavitary pulmonary infarcts.

Figure 8.—(Case 7) Chest film and tomogram showing a thick-walled cavity in the left upper lobe.

blood culture showed hemolytic Staphylococcus aureus, coagulase positive, that was sensitive to methicillin. The arterial blood gases (room air) were pO_2 43 mm and pCO_2 29 mm of mercury, and the pH was 7.54. An x-ray film of the chest showed a round, opaque infiltrate in the right costophrenic sulcus with an adjacent area of discoid atelectasis (Figure 6). The infiltrate was consistent with a septic infarct. The patient responded to methicillin and supportive treatment, with resolution of the infiltrate after three weeks.

Case 6.—(Septic pulmonary embolus from tricuspid valvulitis.) A 24-year-old man was admitted to the hospital with chills, elevated temperature, anorexia, and left lower chest pain of a week's duration. He had been injecting heroin intravenously for the past seven years, the last injection had occurred several days before the present illness. On examination, old and new needle tracks were noted over the antecubital areas. A grade III/VI systolic murmur was heard at the lower sternal border. A systolic ejection click was heard over the pulmonic area as well as a diastolic gallop. Coarse rales were heard over the left lung base. Hematuria was present and blood cultures repeatedly grew Staphylococcus albus and aureus, coagulase positive. A chest x-ray film showed patchy infiltrates in both lung bases with central lucency, suggestive of cavitary pulmonary infarcts (Figure 7). The patient responded to cephalothin therapy with complete resolution of the pulmonary lesions. Extended cephalothin therapy was continued to control the tricuspid valvulitis.

Lung abscess

Lung abscess is a frequent complication of drug addicts,[3] and may be secondary to pneumonia, aspiration pneumonitis or necrotizing pulmonary infarcts. Aerobic microorganisms are chiefly the predominant bacterial agent involved, but anaerobic organisms are often implicated.

Case 7.—A 30-year-old man was admitted to the hospital with complaint of sharp pain in the left anterior chest region and a productive cough with bloody sputum. He admitted to being a heroin user. On examination, old and new needle tracks were noted over both antecubital areas. Rhonchi and crepitant rales were heard over the left upper chest. Sputum culture showed Pseudomonas and Streptococcus viridans (alpha) orga-

Figure 9.—(Case 8) Interstitial nodulo-reticular infiltration in the lower lobes of both lungs.

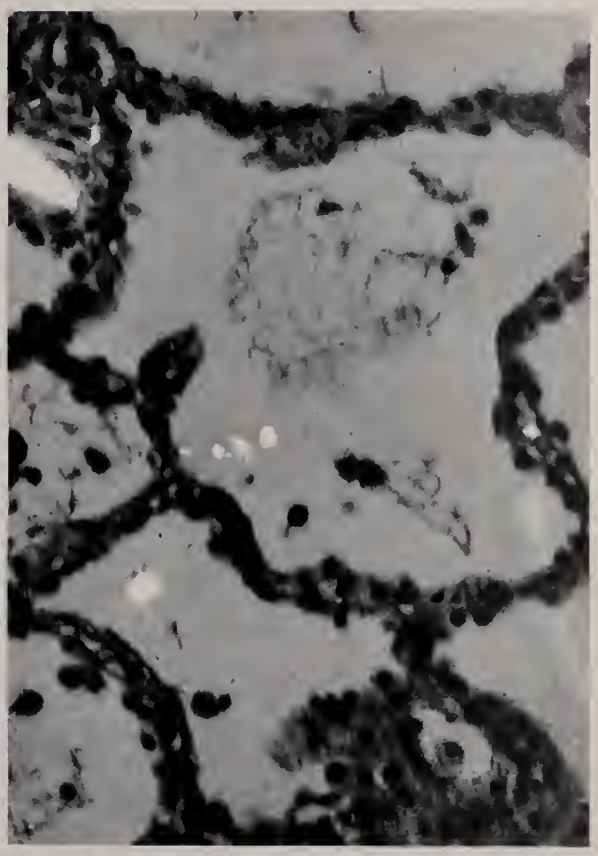


Figure 10.—(Case 8) Biopsy specimen of the right lower lobe showing granulomas and talc crystals by polarized light microscopy.

nisms. A chest x-ray film and tomograms showed a thick-walled cavity in the left upper lobe (Figure 8). With persistent postural drainage, physical therapy, and appropriate antibiotics, supplemented with repeated bronchoscopic drainage, complete resolution of the abscess occurred.

Drug abuse associated with pulmonary fibrosis and pulmonary vascular talc granulomatosis

Pulmonary fibrosis and pulmonary vascular talc granulomatosis are the sequelae of intravenously injected particulates from material used to filter dissolved heroin, or may be the result of intravenous mixtures of dissolved tablets intended for oral consumption.

Case 8.—A 33-year-old man was admitted to the hospital with complaint of a cough and chest pain. He had been a heroin addict and had on frequent occasions intravenously injected mixtures of heroin and dissolved barbiturate or methylphenidate (Ritalin®) tablets. On examination, needle tracks were observed in several locations. Coarse inspiratory rales were heard over the right hemithorax. A chest x-ray film showed an interstitial, nodular-reticular infiltration in the lower lobes of both lungs (Figure 9). On polarized microscopic examination, a trephine (drill) biopsy specimen from the right lower lobe showed arteritis, granulomas and talc crystals in the alveolar and perialveolar areas (Figure 10).

Discussion

Of all the various congeners of heroin that are taken illicitly—morphine, codeine, pantopon and methadone—heroin is the most widely used. The popularity of heroin apparently is related to the easy availability of this drug, particularly in large cities. In heavily populated urban areas, contacts are quickly established to negotiate for the purchase of heroin. Many of the untoward reactions may be traced to this stage of heroin procurement. The street vendor or pusher reduces the potency of the drug by adding various agents—milk sugar, lactose or quinine. The potency is seldom uniform and overdose frequently results from exceeding the user's tolerance. Moreover, sanitary precautions are seldom observed in the "cutting" process, thus increasing the likelihood of septic contaminants. In addition, other agents that are used to cut the drug may have deleterious effects on the

user, notably corn starch, mannite, baking soda, and talc.

Contributing to the increasing incidence of pulmonary complications associated with the heroin drugs is the present vogue of injecting potentiating combinations of drugs and the concomitant use of ethanol. The following intravenous mixtures have been observed in this series: Heroin combined with dissolved oral tablets or capsules containing such drugs as methadone, barbiturates, amphetamines, glutethimide, phenmetrazine hydrochloride, methylphenidate hydrochloride and phencyclidine hydrochloride.

Another important factor in precipitating drug overdose is the loss of tolerance in the addict following a period of withdrawal treatment or abstention; the dose he was previously accustomed to, then may become an overdose.

Complications also occur from the bizarre methods of illicit drug administration. The more common method of taking heroin is the intravenous route ("mainliner"); however, the injection site is seldom made sterile, thereby providing a nidus for hematogenous infections. Heroin is often injected into the skin either subcutaneously or through clothing ("skin popper"). This kind of administration leads to the formation of chronic subcutaneous abscesses, cellulitis, and granulomas. Hepatitis, tetanus, and malaria have also resulted from indiscriminate, unsterile heroin-drug injections. The inhalation of heroin ("snorter") and the smoking of heroin have been associated with overdose and pulmonary edema. Awareness of these forms of administration as well as of the sublingual injection method is important, since needle tracts or skin stigmata may not be evident as diagnostic clues of drug abuse.

The onset of pulmonary edema following heroin-drug overdose is instantaneous in most cases, although in some cases the edema does not appear until 24 to 48 hours after hospital admission and occasionally may develop as the patient emerges from coma. Changes in serial chest x-ray films and sequential arterial blood gases are reliable indicators of pulmonary edema. Alveolar infiltrates that become diffusely confluent with absence of cardiac enlargement and venous congestion would tend to preclude pulmonary edema of cardiac origin. The abrupt appearance of pulmonary edema in a young person without underlying cardiac disease usually is indicative of heroin overdose.

Coma and pulmonary edema may be produced by overdose with a large number of narcotic agents. These drugs include heroin, morphine, methadone, meperidine, hydromorphone, codeine, oxycodone, hydrocodone, diphenoxylate, propoxyphene, and pentazocine. Most addicts prefer heroin.[4]

Narcotic antagonists are important adjuncts in the therapy of heroin and narcotic related overdose. Nalorphine and naloxone are the two most widely used narcotic antagonists; the latter is the drug of choice. Naloxone does not have the agonistic effects induced by nalorphine, which are similar to those of narcotics, namely, respiratory depression, miosis and depression of certain reflexes.[5] Moreover, naloxone is not effective in reversing the depressive effects of non-narcotic agents, barbiturates and phenothiazine tranquilizers; hence it may be utilized as a diagnostic test to exclude suspected opiate overdose. Narcotic antagonists can precipitate pronounced withdrawal symptoms in narcotic addicts and may require prompt counteractive measures.

The pathogenesis of heroin-induced pulmonary edema remains unclear; however, various hypotheses have been advanced. Hypersensitivity and anaphylaxis to the injected material have been suggested as etiologic factors.[6] This theory is plausible to account for the immediate deaths and pulmonary edema from heroin overdose, but does not readily explain the delayed subsequent onset of pulmonary edema. The similarity of heroin pulmonary edema to the pulmonary edema that follows neurogenic disorders such as cerebral tumor, trauma and vascular accidents has led to speculation that the central nervous system is implicated in heroin pulmonary edema.[7] However, the lack of spinal fluid abnormalities in these cases appears to negate a neurogenic association. Adulterant agents commonly used to "cut" the purity of heroin have been suspect of initiating pulmonary edema, either by a toxic or an allergic effect. Quinine, a common "cutting" agent, could have a potentially deleterious action on the heart,[8] but these reactions are not observed with other adulterants. A current theory as to the cause of heroin pulmonary edema underlines the factors of hypoxia, alveolar hypoventilation and increased capillary permeability.[9] The mechanism is analogous to that of high altitude pulmonary edema: Anoxia, depressed respiration, increased capillary

permeability, and extravasation of fluid leading to pulmonary edema.[10] A recent study by Katz and associates[11] suggests that heroin pulmonary edema may be the result of increased capillary permeability with the extravasation of serum into the alveoli, directly related to the opiate and not necessarily due to hypoxia. The pulmonary edema fluid has been reported to have a high protein concentration characteristic of serum.[11,12]

The sequential pathologic features of acute heroin pulmonary edema have been well documented. From cases in which the interval between the intravenous injection and death is known, the following conclusions have been derived.[13] When the time between the intravenous injection of the narcotic and death is within three hours, the lungs at autopsy have a boggy and congested appearance, and numerous foci of atelectasis and emphysema are found. When the interval is three to twelve hours between the lethal injection and death, "narcotic lungs" are noted at autopsy. The lungs are edematous, with a whitish froth filling the air passages. The lobular markings are outlined and patchy areas of emphysema and atelectasis are found in the anterior areas. The alveoli contain fibrin and a hyaline membrane is found in many of the alveoli. After 24 hours, the lungs have a meaty, reddish, granular appearance suggestive of confluent lobular pneumonia.

The physiologic findings of heroin pulmonary edema characteristically represent the features of respiratory depression—decreased ventilation, hypoxemia, hypercapnia, elevation of the alveolar-arterial oxygen gradient and arterial oxygen desaturation. A combined respiratory and metabolic acidosis is frequently associated with heroin pulmonary edema.[14] Pulmonary function tests show a pronounced reduction in total lung capacity, in vital capacity, and in 1-second forced expired volume. The carbon monoxide diffusing capacity is also significantly reduced. Functional impairment may persist for ten to twelve weeks.[15]

Pneumonia appears with greater frequency than might be suspected in patients admitted for drug overdose. Louria and co-workers observed that the susceptibility to pneumonia was related to the duration of heroin use.[16]

The occurrence of aspiration of gastric contents is difficult to ascertain in the absence of residual gastric particulates in the pharynx or around the mouth and nose. Aspiration may be suspected although not yet detectable by chest x-ray or physical findings if significant right to left shunting is present.[17] When the patient is seen shortly after aspiration, bronchoscopic suction and lavage may be helpful, especially if the gastric particulates are large and distributed bilaterally. The availability of the flexible bronchoscope will undoubtedly encourage the more frequent use of this procedure. Steroids and antibiotics are also of benefit in the early stages of aspiration pneumonia.[17,18]

Septic pulmonary emboli linked with intravenous drug abuse usually originate from an area of septic thrombophlebitis in close proximity to an infected injection site, or from the right sided endocarditis. Frequently, septic pulmonary emboli may present as pneumonia with Staphylococcal septicemia.[19] Emboli arising from the tricuspid valve are usually bacterial. The radiologic features of septic pulmonary emboli may vary from small, scattered, consolidated areas simulating bronchopneumonia to round or wedge-shaped opacities.[20] The pulmonary lesions may also be multiple, appearing in one area of the lung and then another.[21] The infarcts may resolve or undergo cavitation and abscess formation. Infrequently, the septic infarct will extend to the pleura, resulting in empyema. With complete resolution of the infarct, the radiologic features may return to normal; occasionally, residual fibrotic, atelectatic areas or pleural thickening persist.

Intravenous multi-drug abuse may result in pulmonary talc granulomatosis. The current trend among drug addicts of combining heroin with dissolved tablets intended for oral use, and injecting these mixtures intravenously, accounts for this manifestation. The more commonly used mixtures include heroin and methylphenidate hydrochloride (Ritalin®), or heroin and dissolved barbiturate or amphetamine tablets. Tablets generally contain a filler substance consisting mainly of talc (magnesium trisilicate) which may produce, when injected intravenously, a granulomatous reaction in the lungs. Often, fibers (from cotton or gauze used to filter the drug mixture) included in the intravenous injection also lodge in the lung. The observed pulmonary granulomas have a characteristic perivascular or intravascular location.[22] Necropsy studies indicate that the larger talc particulates are filtered by the lungs,[23] and they are easily discernible with polarized light microscopy. The chest x-ray films of these patients are suggestive of interstitial pulmonary fibrosis. A reduc-

tion in the carbon monoxide diffusion capacity is found in former addicts and in heroin users with hepatitis. This could be compatible with the possibility that chronic diffusion impairment results from foreign body granulomas in the lung.[24] Talc-induced pulmonary granulomatosis may be instrumental in producing pulmonary hypertension and cor pulmonale.[25]

Pulmonary edema was the major complication in this series. Of 24 patients (10 percent) admitted with pulmonary edema, four died. A higher incidence of pulmonary edema and deaths has been reported in other series. Duberstein and Kaufman[10] noted the ocurrence of pulmonary edema in 71 (48 percent) of 149 patients admitted over a period of 17 months for heroin overdose. Thirteen patients (8.7 percent) died, all 13 had pulmonary edema.

Trade and Generic Names of Drugs

Narcan® ..... naloxone
Nalline® ..... nalorphine
Lasix® ..... furosemide
Ritalin® ..... methylphenidate

REFERENCES

1. Becker CE: Changing medical complications of illicit drug use—Fact or fancy? (Editorial). Calif Med 119:69-70, Aug 1973
2. Mitchison M, Hawks D, Davidson J, et al: Sedative abuse by heroin addicts. Lancet 1:606-607, 1970
3. Cherubin CE: The medical sequelae of narcotic addiction. Ann Intern Med 67:23-32, 1967
4. Stimpson FV, Ogborn AC: A survey of addicts prescribed heroin at London Clinics. Lancet 21:1163-1166, 1970
5. Martin WR: Opioid antagonists. Pharmacol Rev 19:463-521, 1967
6. Helpern M, Rho YM: Deaths from narcotism in New York City. NYJ Med 66:2391-2408, 1966
7. Luisada A: Paroxysmal pulmonary edema and the acute cardiac lung. Am J Cardiol 20:69-76, 1967
8. Lupovich P, Pilewski R, Sapira JD, et al: Cardiotoxicity of quinine as adulterant in drugs. JAMA 212:1216, 1970
9. Steinberg AD, Karliner JS: The clinical spectrum of heroin pulmonary edema. Arch Int Med 122:122-127, 1968
10. Duberstein JL, Kaufman DM: A clinical study of an epidemic of heroin intoxication and heroin-induced pulmonary edema. Am J Med 51:704-714, 1971
11. Katz S, Aberman A, Frand UI, et al: Heroin pulmonary edema—Evidence for increased capillary permeability. Am Rev Resp Dis 106:472-474, 1972
12. Frand UI, Shin CS, Williams MH: Methadone-induced pulmonary edema. Ann Int Med 76:975-979, 1972
13. Siegel H: Human pulmonary pathology associated with narcotic and other addictive lungs. Human Pathology 3:55-73, 1972
14. Frand UI, Shin CS, Williams MH Jr: Heroin induced pulmonary edema. Ann Int Med 77:29-35, 1972
15. Karliner JS, Steinberg AD, Williams MH Jr: Lung function after pulmonary edema associated with heroin overdose. Arch Intern Med 124:350-353, 1969
16. Louria DB, Hensle T, Rose J: The major medical complications of heroin addiction. Ann Int Med 67:1-22, 1967
17. Mann JB, Sandberg DH: Therapy of sedative overdosage. Ped Cl No Amer 17:617-628, 1970
18. Hamelberg W, Bosomworth PP: Aspiration pneumonitis—Experimental studies and clinical observations. Anesth Analg 43: 669-677, 1964
19. Briggs JH, McKerron CG, Souhami RL, et al: Severe systemic infections complicating "mainline" heroin addiction. Lancet 2:1227-1231, 1967
20. Hussey HH, Katz S: Septic pulmonary infarction: Report of 8 cases. Ann Int Med 22:526-542, 1945
21. Jaffe RB, Koschmann EB: Intravenous drug abuse, pulmonary, cardiac, and vascular complications. Am J Roent Rad Th Nuc Med 109:107-120, 1970
22. Hopkins GB, Taylor DG: Pulmonary talc granulomatosis. Amer Rev Resp Dis 101:101-104, 1970
23. Hahn HH, Schweid AI, Beaty HN: Complications of injecting dissolved methylphenidate tablets. Arch Intern Med 123: 656-659, 1969
24. Wendt VE, Puro HE, Shapiro J, et al: Angiothrombotic pulmonary hypertension in addicts. JAMA 188:755-757, 1964
25. Hopkins GB: Pulmonary angiothrombotic granulomatosis in drug offenders. JAMA 221:909-911, 1972

Refer to: Afonso JF: Mixed mesodermal tumors of the uterus.
West J Med 120:17-26, Jan 1974

Mixed Mesodermal Tumors of the Uterus

JOSE F. AFONSO, MD, *Hayward, California*

Two of five women with mixed mesodermal tumor of the uterus are well more than ten years after therapy. A third was well when last seen two years after therapy and died at age 84 but autopsy was not done.

Review of the literature and the reported experience indicates that this diagnosis should be suspected more often. Since histologic features may vary from one place to another within the lesion, accurate assessment requires examination of adequate specimens of the tumor. The mere presence of heterologous elements in an endometrial carcinoma changes the five-year survival rate from 85 percent to less than 35 percent. While total abdominal hysterectomy with bilateral salpingo-oophorectomy is mandatory, radiation therapy should be added more often than in the past, as it has been clearly shown that many of these tumors are radiosensitive.

MIXED MESODERMAL TUMORS of the uterus are considered to be among the most malignant of neoplasms. Although they are relatively rare, accounting for only 0.2 percent or fewer of all gynecologic hospital admissions,[1] they derive clinical importance from an association with previous radiation therapy, and from the success of treatment in a number of cases.

The classification of these neoplasms has been controversial ever since Kehrer[2] proposed the term *mixed mesodermal tumor* in 1906. By 1935, McFarland[3] had collected 119 names representing attempts to designate the gross or microscopic features in individual cases. The basic neoplastic element is mesenchymal sarcoma, often called "undifferentiated cellular sarcoma," "endometrial sarcoma," or "fibromyxosarcoma." Other histologic components appear as discrete islands surrounded by the sarcomatous background. In various tumors, and in areas of the same tumor, there may be rhabdomyosarcoma, chondrosarcoma, leiomyosarcoma, fibrosarcoma or liposarcoma, singly or in diverse combinations. Carcinomatous elements are also frequent; the most common is endometrial carcinoma, but epidermoid, papillary or mucinous adenocarcinoma is often present.

The degree of differentiation and the relative proportions of all elements vary widely. One histologic component may so predominate that if an insufficient sample is obtained, the tumor may be misdiagnosed according to that single element.

Zenker,[4] in 1864, classified as "pure" those

From the Department of Obstetrics and Gynecology, Kaiser-Permanente Medical Center, Hayward.

Submitted April 3, 1973.

Reprint requests to: J. F. Afonso, MD, Kaiser-Permanente Medical Center, 27400 Hesperian Boulevard, Hayward, CA 94545.

TABLE 1.—*Comparative Frequency of Mixed Mesodermal and Other Malignant Tumors of the Uterus*

Report by	Mixed Mesodermal	Carcinoma	
		Cervix	Endometrium
Symmonds and Dockerty, 1959[9]	1	345	143
Krupp et al, 1961[10]	1	120	14
Edwards et al, 1963[11]	7	...	475
Falkinburg et al, 1964[12]	1	...	30
Mortel et al, 1970[13]	9	...	150

TABLE 2.—*Reported Cases of Mixed Mesodermal Tumors of the Uterus*

Report by	Number of Cases	Year
Speert and Peightal[14]	4	1949
McElin and Davis[15]	2	1952
Schiffer, Mackles, and Wolfe[16]	5	1955
Taylor[17]	26	1958
Ober and Tovell[18]	12	1959
Ricciutti, Noble, and Kiefer[19]	1	1961
Heinrichs, Climie, and Cook[20]	1	1962
Edwards et al (review)[11]	295	1963
Falkinburg et al[12]	6	1964
Rachmaninoff and Climie[21]	30	1966
Chaves[22]	3	1966
Norris, Roth, and Taylor[23]	31	1966
Mendel, Lucas, and Panopio[24]	15	1967
Persaud and Knight[25]	4	1968
Gudgeon[26]	1	1968
Ruffolo, Metts, and Sanders[27]	9	1969
Masterson and Kremper[28]	25	1969
Edwards[29]	85	1969
Chuang, Van Velden, and Graham[1]	20	1970
Glover[30]	1	1970
Mortel et al[13]	9	1970
Reddy, Bharma, and Sankaran[31]	1	1970
Schaepman-Van Guens[32]	29	1970
Giarratano and Slate[33]	4	1971
Total	499	

mesenchymal sarcomas that are composed of a single cell type; as "mixed," those comprising more than one cell type. He classified as "homologous" those made up of tissue elements indigenous to the uterus, and as "heterologous" those containing tissue elements normally foreign to the uterus. On this basis, Ober,[5] in 1958, proposed an elaborate but clear classification of mesenchymal sarcomas, useful where an adequate specimen is properly studied. According to that classification, any uterine cancer that contains stromal sarcoma plus one or more heterologous elements, or that contains two or more heterologous elements, should be coded "mixed mesodermal tumor." The carcinomatous components of mixed mesodermal tumors, unlike the sarcomatous elements, are limited by the potentialities of the müllerian tract.

Mixed mesodermal tumors characteristically originate in the stroma of the genital tract, immediately beneath the lining epithelium, which is frequently intact. They are often of multicentric origin, and seem never to arise deep within the uterine wall. Of the two main hypotheses that have been advanced for their histogenesis, the cell rest theory suggested by Cohnheim[6] in 1875 is incompatible with modern concepts of carcinogenesis. In 1892, Pfannenstiel[7] proposed that they arise by metaplasia from uterine mesodermal tissue. It is now generally believed that they arise in situ from endometrial[8] and endocervical stroma. This, the most primitive uterine tissue, has in common with other mesenchymal cells the ca-

TABLE 3.—*Patient Characteristics and Presenting Manifestations*

Patient	Race	Age	Gravida/ Para/ Abortions	Marital Status	Interval Since Last Menstrual Period	Past History and Presenting Manifestations
1	White	53	3/2/1	Married	3 Weeks	Normal menstrual history. Watery vaginal discharge 3 months
2	White	41	0	Single	5 Days	Normal menstrual history. Persistent intermenstrual vaginal spotting 5 months. 5 days after onset of last menstrual period, low abdominal cramps; passed tissue 12.5 × 7.5 × 3.5 cm per vagina; diagnosed leiomyosarcoma
3	White	82	5/5/0	Widowed	30 Years	Intermittent slight vaginal bleeding 8 months
4	White	61	0	Single	13 Years	During anticoagulant therapy for thrombophlebitis 6 months ago, vaginal spotting; persisted. Heavy vaginal bleeding 4 days ago, 2 to 3 soaked towels daily. Lost 20 pounds preceding year. Treated for diabetes mellitus 7 years; for arteriosclerotic cardiovascular disease with congestive heart failure 6 months. Right oophorectomy, tubal ligation 30 years ago
5	Black	64	4/3/1	Married	15 Years	Gush of bright red blood per vagina 3 months ago; then persistent vaginal bleeding (2 to 3 pads daily) and foul vaginal discharge. Lost 45 pounds preceding year

pacity to differentiate into many mesenchymal derivatives (striated muscle, cartilage, fat) as well as into epithelial structures characteristic of the müllerian tract. This is understandable when we recall that, except for its nerves, the entire uterus is of mesodermal origin.

The rarity of mixed mesodermal tumors relative to the occurrence of other malignant tumors of the uterus as reported by several observers[9-13] is apparent from Table 1. Only 499 cases appear to have been reported hitherto[11-30,31-33] (Table 2). Added to those are the five cases whose salient features are summarized in Tables 3, 4 and 5 in lieu of individual case reports.

Some investigators have suggested that race, parity, or sexual activity may correlate with the incidence of these tumors. It has been proposed that they occur more often in blacks than in whites;[23,36] and the reverse has been observed.[1] The same contradictions can be found with regard to parity and sexual activity.[1,9,15]

Site of Origin Related to Menstrual Status

The most common site of origin of mixed mesodermal tumors of the uterus is the corpus, where they are found almost exclusively in menopausal and postmenopausal women. This diagnosis is occasionally made during adolescence but seldom during the reproductive years. In women of this age range, mixed mesodermal uterine tumors usually start in the cervix. During infancy and childhood, the juvenile member of this family of tumors, botryoid sarcoma, usually begins in the vagina.

Patient 1 of the present report was 53 years of age and still menstruating; the tumor had its origin in the cervical stroma. In Patients 2 to 5, the tumor began in the endometrial stroma.

Mixed mesodermal tumors, as well as carcinosarcomas, have been reported as primary ovarian tumors; but this is extremely rare, and such neoplasms are believed to originate in areas of endometriosis.[34,35]

Radiation Therapy: Possible Etiologic Factor

The majority of the uterine neoplasms that arise after radiation therapy are mixed mesodermal tumors or carcinosarcomas. Although a causative relation cannot be established because the cases have been few, follow-up data are incomplete and many variables are involved, an association between the appearance of mixed mesodermal tumors and previous radiation to the pelvis has been reported by many observers. The carcinogenic activity of radiation appears to be greater with small than with large doses; neoplasia therefore more often follows such treatment for benign than for malignant lesions. Thirty-six (10 percent) of the 360 patients listed in Table 6 had received radiotherapy for benign lesions; 14 (3.8 percent) for other malignant neoplasms. The intervals between radiotherapy and the diagnosis of mixed mesodermal tumor ranged from four years to 36 years, except that one tumor developed a year after radiation for benign disease[24] and another arose while the patient was receiving chemotherapy after radiation for ovarian cystadenocarcinoma.[26] None of the five patients of the present series had received radiotherapy in the past.

Since an association does exist and the interval between exposure and the appearance of the tumor may be long, patients who have received radiation therapy to the pelvic region should be observed periodically longer than 20 years with the possibility of postirradiation cancer in view. In treating younger women for cancer, whenever the cure rates of radiotherapy and surgical excision are equivalent, the latter should be chosen. It is heartbreaking to find a mixed mesodermal tumor or carcinosarcoma of the uterus ten or more years after the apparent cure of another gynecologic cancer.

Signs and Symptoms

The manifestations of mixed mesodermal tumor are nonspecific. Abnormal vaginal bleeding is the presenting complaint of 80 to 90 percent of patients with this disease. Crampy lower abdominal pain, foul watery or purulent vaginal discharge, passage of fragments of necrotic tissue per vagina, and weight loss are frequent. Three of the patients in the present series had postmenopausal bleeding; one had only watery vaginal discharge, and another had intermenstrual bleeding with cramps in the lower part of the abdomen.

Pelvic examination often leads to prompt consideration of this diagnosis, as in 30 to 50 percent of the cases a polypoid tumor protrudes from the cervical os or within the cervical canal or, occasionally, through the vaginal introitus. Mixed mesodermal tumors are frequently bulky, friable, soft and fleshy, fungating and occasionally necrotic, reddish purple or whitish gray. In many instances, however, the only abnormal finding is uterine enlargement, with or without irregularity of contour; for early lesions, the findings are usually normal.

TABLE 4.—*Pertinent Findings on Initial Examination**

Patient	*Physical Examination*	*Pelvic Examination*	*Papanicolaou Smear*	*Biopsy*	*Roentgenography*†
1	Normal	Pedunculated whitish-gray mass protruded from cervical os	....	.....	.....
2	Irregular, nontender, globular, firm pelvic mass to 7 cm above symphysis pubis	Reddish-purple polypoid mass protruded from cervical os; os dilated to 1.5 cm. Uterine fundus anteverted, freely movable, globular, 16-weeks gestation size	Class I	Chronic cervicitis	Routine views normal
3	Well-nourished, healthy. Firm, regular, movable, tender mass, lower abdomen to 11 cm above symphysis pubis	Necrotic, cyanotic, 4 × 3 × 3-cm mass protruded through external cervical os; os 2 cm dilated. Cervix bled easily on contact. On bimanual examination, cervix firm, dilated 2 cm around firm mass. Uterine fundus irregular, firm, mobile, 16-weeks gestation size	Class I	*Cervix:* normal. *Protruding mass:* endocervical polyp. *D&C:* 350-gm soft, grayish, multinodular tissue: mixed mesodermal sarcoma	Routine views, skull films, barium enema normal. Excretory urography showed large soft-tissue pelvic mass
4	Obese; BP 200/100; mild cardiomegaly; optic fundi Keith-Wagner grade ii.	6 × 3-cm exophytic, pedunculated, friable, hemorrhagic mass arising from middle ⅓ of posterior vaginal wall protruded through vaginal introitus. Cervix slightly dilated; polypoid, friable tissue through external os. Uterine fundus anteverted, 8-weeks gestation size. Adnexae poorly outlined. No palpable masses	Class II	*Mass at vaginal introitus:* necrotic hemorrhagic tissue. *Vaginal lesion:* pleomorphic neoplasm, adenoid, sarcomatoid, anaplastic elements. Giant and multinucleated cells; cells suggesting myogenic differentiation. *Diagnosis:* mixed mesodermal tumor	Plain film of abdomen, barium enema, excretory urogram, lateral view of lumbosacral spine normal. *Chest:* 2 nodules, 1 × 2 cm, in each lung field
5	Confused, lethargic, obese; BP 160/90; pulse 90; cataract left eye. Firm, fixed, nontender mass, lower abdomen to 2 cm above umbilicus	Perineum covered with foul-smelling, feces-like vaginal discharge. Cervix not identifiable. Tongues of necrotic tissue filled vaginal apex, protruded into vaginal canal. Pelvic cavity filled wall-to-wall with hard, fixed mass (frozen pelvis) to umbilicus	....	.....	Chest: normal

*Findings in blood and urine were normal or nonspecific for this disease. In Patient 4, electrocardiogram showed left axis deviation, digitalis effect. Patient 5's urine was loaded with white and red blood cells and bacteria; hematocrit 31 percent; leukocyte count 21,200; blood urea nitrogen 148 mg per 100 ml; other abnormalities of blood chemistry typical of terminal disease.

†Chest film, excretory urography, and lateral view of lumbosacral spine are here designated "routine."

In other cases, the entire pelvic contents appear to be replaced by tumor. The ascites, cachexia, and masses throughout the abdomen which are seen in advanced disease suggest ovarian cancer. Thus, in a large proportion of patients, the results of the physical examination are not diagnostic of mixed mesodermal tumor.

Pathologic Findings

Gross Appearance

A polypoid growth usually fills the endometrial cavity. The tumor mass may be single or multiple; its consistency may vary from fairly firm to soft and fleshy. The base of the tumor may be broad or narrow, but demarcation from the underlying myometrium is usually distinct. As in Patient 3 of this report, the tumor may appear as globular, firm elevations of the endometrial surface measuring less than a centimeter in diameter.

Although there is no causal relation between uterine leiomyomata and mixed mesodermal tumors, they often coexist. The finding of a soft polypoid mass within a uterine cavity containing leiomyomata may lead one to assume erroneously that a submucous fibroid tumor has undergone degeneration or malignant change.

The cut surface of a mixed mesodermal tumor is usually soft and moist and grayish white, pinkish or purple; there are usually hemorrhage and necrosis; occasionally there are areas of gelatinous softening or cyst formation.

Microscopic Appearance

The background of the varied histologic structure that is presented by mixed mesodermal tumors is endometrial sarcoma, characterized by poorly differentiated cells with sparse cytoplasm, crowded nuclei, and indefinite borders. Within this basic neoplasm, tissue or tissues are found which have no benign counterpart in the uterus (heterologous). Of these, striated muscle and cartilage are encountered most commonly.

In the opinion of a minority of observers,[41] the *sine qua non* for the diagnosis of mixed mesodermal tumor of the uterus is the presence of embryonal myoblasts. Some investigators insist on the presence of typical longitudinal and transverse striations, permitting identification of the cells as being of striated muscle origin. The majority,[1,28,39,44] however, accept as sufficient proof the presence of numerous pleomorphic cells with abundant eosinophilic cytoplasm having a "strap" or "tadpole" shape. The tissue culture studies of Murray and Pogogeff[42,43] showed that spindle cells with intensely eosinophilic and perhaps granular cytoplasm are embryonic rhabdomyoblasts in a stage of development preceding the development of cross striations.

If one accepts Ober's classification,[5] the presence of carcinomatous elements, whether squamous or adenoid, will place the tumor in the category, carcinosarcoma with heterologous elements. Most other investigators[1,13,28,39] define carcinosarcomas as those tumors which are composed only of sarcomatous and carcinomatous elements; they reserve the term *mixed mesodermal tumor* for those which contain, in addition, heterologous elements.

Some observers[10,21,44] consider such a distinction to be valueless because the clinical features, treatment, prognosis and gross pathologic features of these two types of cancer show no significant differences. Others[23,32] have found sufficient behavioral differences to continue the separate classifications on the basis of their definitive microscopic features. Schaepman-Van Geuns[32] reported a 14 percent better survival rate associated with carcinosarcomas than with mixed mesodermal tumors.

Mode of Spread

Mixed mesodermal tumors invade surrounding tissues by continuity, through lymphatic channels, and through the blood stream, as indicated by study of the tumor and surrounding tissues, the appearance of metastasis, and the sites of recurrence. Some observers[1,13,28] have found that the soft tissues and lymph nodes of the pelvis are involved in most patients, and that local recurrence is frequent. Others[10,21] have emphasized that distant metastasis is the rule rather than the exception, and that hematogenous spread is more frequent than lymphatic. The most common sites of metastasis are the lungs, pleura, vagina, omentum, mesentery, ovaries and extrapelvic lymph nodes. One or more tissues seen in the primary tumor may occur in the metastatic site, so that either or both of the sarcomatous and carcinomatous elements may be clearly distinguished.

Diagnosis

Because the majority of patients complain of abnormal uterine bleeding, dilatation and curettage is a frequent diagnostic procedure. In 25 to 50 percent of the cases, the diagnosis of mixed

TABLE 5.—*Treatment, Gross and Microscopic Findings, and Outcome*

Patient	*Treatment*	*Gross Appearance of Tumor*	*Microscopic Findings*	*Outcome*
1	(a) Tumor exised; scalpel conization of cervix; dilatation and curettage	Smooth outer cover. Cut surface coarsely lobulated, uniformly gray; brain-like consistency	Round cell sarcoma, areas of myxosarcoma and adenocarcinoma; in other areas stromal sarcoma, chondrosarcoma, adenocarcinoma merged (Figure 1). Endometrial cuttings normal. *Conization specimen:* cervical stroma infiltrated by adenocarcinoma	.....
	(b) Radium (5 Carmel applications, each with 10 mg of radium, 2 vaginal ovoids, each with 25 mg of radium = 5,000 r to Point A). Six weeks later, total abdominal hysterectomy with bilateral salpingo-oophorectomy. Postoperative cobalt = 4,000 rads to pelvic midplane	At hysterectomy, slight uterine enlargement only visible abnormality	Necrotic endometrium, myometrial infiltration by adenocarcinoma to serosa; extensive perivascular and lymphatic invasion. Cervix infiltrated by glandular carcinoma; tumor within lymphatic vessels	Patient well, no recurrence, 11 years and 6 months after hysterectomy
2	Total abdominal hystrectomy, bilateral salpingo-oophorectomy	Uterine fundus 16-18 weeks' gestational size; leiomyoma on posterior surface. Right ovary 6 × 3.5 × 4 cm; left normal. In opened uterus, fungating, polypoid, necrotic, racemose mass arising from left side. Uterine wall contained many leiomyomata	*Uterine and ovarian tissue:* anaplastic sarcoma cells, large undifferentiated cells suggestive of embryonic muscle cells, nests of squamous cell carcinoma, myxosarcoma. Neoplasm apparently originated just beneath endometrium; minimal myometrial invasion	Patient well, 10 years after hysterectomy
3	Total abdominal hysterectomy, bilateral salpingo-oophorectomy	Uterus 12 weeks' gestational size. Many 3 × 2 cm subserous leiomyomata. Endometrial surface: many globular elevations 0.5 cm greatest diameter. Tubes, ovaries normal	*Endometrial nodules:* pleomorphic spindle-shaped cells, adenocarcinoma, some rhabdomyoblasts, typical tadpole cell (Figure 2). No myometrial invasion	No recurrence 2 years later. Died 1 month later (age 84); no autopsy
4	Desmethylcolchicine, 0.5 mg/kg i.v., 6 days; 2 days interruption, repeated 3 days. Toxic, ineffective. Transvaginal x-ray, 2,400 r in air over 9 days: 3 weeks later, vaginal lesion had melted away, but many minute, easily bleeding polypoid lesions in posterior vaginal wall. Local radium to vaginal mucosa, 4,155 r: one month later, vagina scarred, stenosed, no visible or palpable tumor; chest lesions larger. 5-Fluorouracil: slight, transient decrease in pulmonary nodule size, no apparent effect on primary tumor; toxic (WBC 1,400/mm^3)	*Autopsy:* 1 × 4 cm pearly white nodules throughout both lungs and peritoneal cavity; left adrenal gland replaced by tumor; uterus replaced by 20 × 30 cm, soft, necrotic mass; tubes and ovaries involved	*Uterine tumor:* pleomorphic sarcoma, adenocarcinoma, embryonic rhabdomyoblasts. *Pulmonary metastatic lesions:* exclusively stromal sarcoma	Died 7 months after admission (pelvic mass above umbilicus; ascites; dyspnea)
5	.....	*Autopsy:* pelvic tumor 2 cm above umbilicus replaced uterine fundus. Fallopian tubes normal; ovaries atrophic. Uterine fundus: many leiomyomata; cavity filled with polypoid, soft tumors arising near endocervix, extending into vaginal canal. Bilateral ureteral obstruction; no rectal involvement	*Polypoid tumors:* undifferentiated stromal sarcoma with many giant cells, typical tadpole cells (rhabdomyoblasts). *Other areas:* adenocarcinoma in thick tongues of tissue surrounded by fibrosarcoma.	Died of anemia 3 days after admission

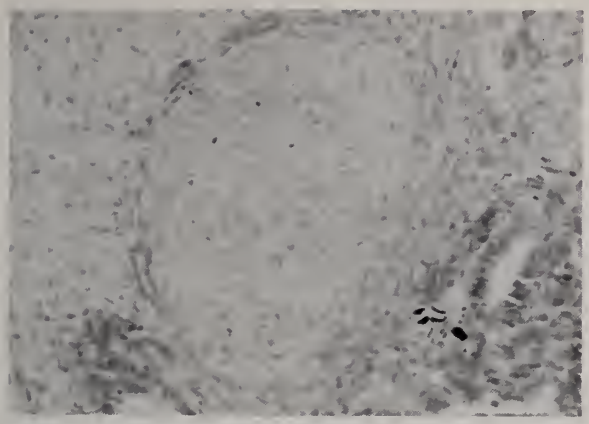


Figure 1.—Merging areas of stromal sarcoma, adenocarcinoma, and chondrosarcoma.

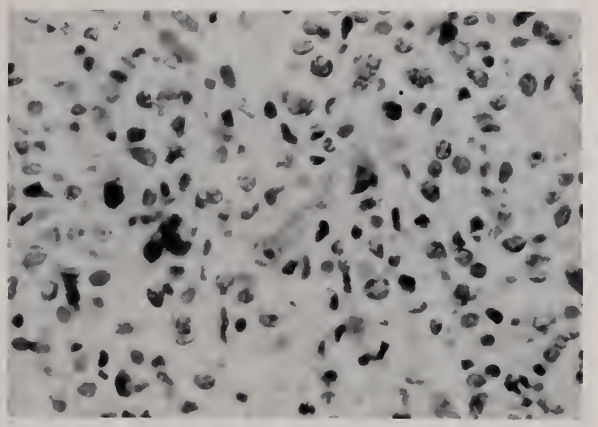


Figure 2.—Stromal sarcoma with typical "tadpole" cells representing rhabdomyoblasts.

mesodermal tumor is missed by this method,[1,28] but the presence of malignant neoplasia is established. Endometrial sarcoma or adenocarcinoma is the most frequent initial diagnosis. Biopsy of the mass that protrudes through the cervical os frequently yields the necessary information, but in many cases only sarcomatous or carcinomatous elements, or what appears to be pure leiomyosarcoma is found, and occasionally there is so much necrosis that no structure can be identified with certainty. In a large number of patients the diagnosis of carcinosarcoma is made, and is changed only after extensive recutting of the specimens with painstaking review of new slides, where heterologous cells are finally found. Often the correct diagnosis is made only after hysterectomy or at autopsy.

Treatment

Review of reported cases shows that a multitude of treatments have been used, all with poor results. Often no treatment was possible or only palliation could be used. The preferred approach is surgical; the minimal procedure contemplated should be total hysterectomy with bilateral salpingo-oophorectomy. If the tumor has originated in or extended to the cervix, radical hysterectomy with pelvic lymphadenectomy is indicated. A few investigators[10,23,36,38] have advised radical hysterectomy with pelvic lymphadenectomy as the initial surgical procedure, irrespective of cervical involvement. The value of regional lymph node removal is questioned by those who believe that these tumors tend to metastasize through the blood rather than the lymph. Two of the patients in the series here reported are living and well more than ten years after total abdominal hysterectomy with bilateral salpingo-oophorectomy; one also received radiation therapy—preoperatively with radium, and postoperatively with cobalt. Patient 3 was treated by total abdominal hysterectomy with bilateral salpingo-oophorectomy alone, and two years later appeared to be free of disease. She died a month after having been seen, at the age of 84.

Some observers[27,32] have expressed serious reservation about the value of radiation therapy, preoperatively or postoperatively, for this disease. Others[10,21,23,25,36,38,45] appear convinced that mixed mesodermal tumors are radioresistant, and that preoperative radiation merely delays treatment; still others,[13,29] that radiation should be added to the surgical procedure either preoperatively[13,29] in the form of radium therapy, or postoperatively as external radiation.[9,12,18] Chuang and colleagues[1] found that neither preoperative nor postoperative radiation affected five-year survival rates, whereas Edwards[29] reported a significant improvement with preoperative radium therapy, and Mortel and coworkers[13] pointed out that, of 26 previously reported patients who had survived five years, 18 had received some form of radiation therapy.

There is no question that some mixed mesodermal tumors are sensitive to radiation.[13,20,29] Kempers, in discussing the paper by Masterson and Kremper,[28] mentioned one patient who had received only palliative irradiation, then lived six and a half years with clinical regression of the tumor. One of the two five-year survivors reported by Edwards and colleagues[11] was treated for recurrence of tumor in the parametrium after subtotal hysterectomy, by local perfusion with gold, irradiation with radium, external radiation and nitrogen mustard. The response in the vaginal

TABLE 6.—*Role of Radiation Therapy in the Development of Mixed Mesodermal Tumors*

Report by	Number of Patients	Previous Radiation: Benign Lesion	Previous Radiation: Malignant Disease	Interval (years)
Chuang et al[1]	20	..	3	7-29
Krupp et al[10]	51	..	2	11-13
Edwards et al[11]	7	1	2	6-10
Mortel et al[13]	9	1	..	28
Speert and Peightal[14]	4	3	..	9-14
McElin and Davis[15]	2	2	..	11-20
Schiffer et al[16]	5	1	..	6
Taylor[17]	40	3	..	?
Ober and Tovell[18]	12	1	..	?
Heinrichs et al[20]	1	..	..	....
Rachmaninoff and Climie[21]	30	..	..	....
Norris et al[23]	31	6	3	7-26
Mendel et al[24]	15	1	..	1
Gudgeon[26]	1	..	1	1.5
Ruffolo et al[27]	9	1	..	?
Masterson and Kremper[28]	25	3	2	4-23
Reddy et al[31]	1	..	..	....
Schaepman-Van Guens[32]	29	3	1	7-31
Sternberg et al[36]	21	..	..	....
Aaro et al[37]	26	6	..	4-36
Hill and Miller[38]	4	2	..	10-11
Marcella and Cromer[39]	11	1	..	6
Rubin[40]	1	1	..	?
Present series	5	..	..	....
Totals	360	36	14	

lesion of Patient 4 of the present series also indicates radiosensitivity.

Radiation alone is used for palliation, as are various forms of chemotherapy. Nitrogen mustard and thioTEPA have been found ineffective.[10,11,36,39] In one reported patient,[26] the tumor developed during chlorambucil therapy; in another, 5-fluorouracil had no apparent effect.[11] Worthwhile palliation has been reported with cyclophosphamide,[28,32] but Glover,[30] using it in a single case, saw no benefit from this drug. In our Patient 4, neither desmethylcolchicine nor 5-fluorouracil afforded significant palliation.

Prognosis

Although extremely poor, the prognosis is not entirely hopeless. Determination of accurate five-year survival rates from reported cases is impeded by the short time elapsing between treatment and report in many instances, by loss of patients to follow-up, and by the inclusion of carcinosarcomas in some series. Excluding those series in which no patient survived as long as five years, Table 7 shows the numbers and percentages of five-year survivors in the 15 remaining reports, and the types of treatment given. The five-year survival rates ranged from 9 percent to 40 percent for an average of 21.3 percent (57 of 267 patients). When series in which all patients died within five years* are included, only 57 of 362 patients (15.7 percent) had this outcome. No conclusion can be drawn with regard to the effectiveness of the type of treatment employed, as it is not clear how many patients in each category died, were lost to follow-up, or had received therapy less than five years previously.

Search for factors that would serve as reliable prognostic indices has elicited some contradictory findings, as well as observations confirmed by most observers. Chuang and coworkers[1] saw no correlation between the number of mitoses per high-power field and survival rates, and noted that a history of irradiation for cancer suggested an extremely poor prognosis. Edwards and colleagues[11] saw no relation between duration of symptoms or early diagnosis and outcome. Survival rates appear to be higher in younger than in older women.[21,32] The influence of specific heterologous elements on survival has been evaluated with contradictory results. The presence of cartilage has been considered a bad prognostic sign by some,[25,47] a good prognostic sign by others,[23] and of no significance by most.[1,28,32] The prognosis is not unfavorably influenced by the presence of a rhabdomyosarcomatous component.[1,21,32]

The two most important prognostic factors are the degree of myometrial infiltration and the extent to which tumor involves other structures. It is interesting, however, to note that all of the four long-term survivors reported by Masterson and Kremper[28] had microscopic invasion of the blood vessels, and one had extension to the uterine serosa.

Our two surviving patients (Patients 1 and 2) were relatively young—41 and 53 years of age; one had extension of the tumor to the right ovary, the other to the uterine serosa with extensive perivascular and lymphatic invasion. One had had symptoms for three, the other for five months before first examination. Cartilage was present in only one. In Patients 4 and 5, who died, the disease was extensive and beyond hope of cure when they were first seen.

The majority of recurrences take place within the first year, but some have appeared three to five years after treatment of the first tumor. The majority of reported patients who died of the dis-

*References 10,16,19,20,26,27,30,33,36,40

TABLE 7.—*Treatment and Five-year Survivals in Series of Patients Followed for at Least Five Years*

Report by	*Number of Patients*	*Radical Hysterectomy*	*TAH**	*TAH, BSO†*	*Preoperative Radiation, TAH, BSO*	*TAH, BSO, Postoperative Radiation*	*Preoperative & Postoperative Radiation TAH, BSO*	*Subtotal Hysterectomy, Radiation*	*Radiation Only*	*Five-year Survivals*	
										No.	*Percent*
Chuang et al[1]	20	..	..	2	..	..	..	..	..	2	12
Symonds and Dockerty[9]	19	..	..	2	..	2	..	..	..	4	21
Edwards et al[11]	7	..	..	..	1	..	..	1‡	..	2	28
Falkinburg et al[12]	6	..	..	1	..	..	..	..	..	1	16
Mortel et al[13]	7	..	..	..	..	..	..	..	1	1	14
Taylor[17]	26	1	..	1	..	..	..	1§	..	3	11
Rachmaninoff and Climie[21]	28	..	2	..	..	3	..	..	1	6	21
Norris et al[23]	31	..	1	1	4	..	..	..	..	6	19
Masterson and Kremper[28]	25	..	..	2	1	1	..	..	..	4	15
Edwards[29]	34	..	..	2	9	..	..	..	..	11	32
Schaepman-Van Guens[32]	33	..	1	9	..	..	..	..	..	10	33
Marcella and Cromer[39]	11	1	..	..	..	..	..	..	..	1	9
Vellios et al[40]	9	..	..	..	3	..	..	..	..	3	33
Carter and McDonald[45]	6	..	..	..	..	1	..	..	..	1	16
Present series	5	..	..	1	..	..	1	..	..	2	40
Totals	267	2	4	21	18	7	1	2	2	57	21.3

*Total abdominal hysterectomy.
†Bilateral salpingo-oophorectomy.
‡Patient also received nitrogen mustard and perfusion with gold, in addition to radium and x-ray.
§Local removal followed by x-ray and radium therapy.

ease had lived eight to twelve months after diagnosis.

It is clear that the diagnosis of mixed mesodermal tumor of the uterus should be suspected more often, and that adequate biopsy specimens should be taken from uterine tumors which may be of this type to allow for accurate diagnosis. In view of the evidence that many mixed mesodermal tumors are radiosensitive, radiation therapy should be used more frequently in treating them.

REFERENCES

1. Chuang JT, Van Velden DJJ, Graham JB: Carcinosarcoma and mixed mesodermal tumor of the uterine corpus—Review of 49 cases. Obstet Gynecol 35:769-780, May 1970

2. Kehrer E: Uber heterologe mesodermale Neubildungen der weiblichen Genitalien. Monatschr f Geburtsh u Gynäk 23:646-681, 1906

3. McFarland J: Dysontogenic and mixed tumors of the urogenital region. Surg Gynec Obstet 61:42-57, Jul 1935

4. Zenker FA: Uber die Veränderungen der willkürlichen Muskeln im Typhus abdominalis: Nebst einem Excurs über die pathologische Neubildung quergestreiften Muskelgewebes. Leipzig, FCS Vogel, 1864, pp 84-86

5. Ober WB: Uterine sarcomas: histogenesis and taxonomy. Ann New York Acad Sci 75:568-585, Jan 9 1959

6. von Conheim J: Congenitales quergestreifter Muskelsarcom der Nieren. Arch path Anat Physiol 65:64-69, 1875

7. Pfannenstiel J: Das traubige Sarcon der Cervix uteri. Virchows Arch path Anat 127:305-337, 1892

8. Papanicolaou GN, Maddi FV: Observations on the behavior of human endometrial cells in tissue culture. Am J Obstet Gynecol 76:601-618, Sep 1958

9. Symmonds RE, Dockerty MB: Sarcoma and sarcoma-like proliferations of the endometrial stroma. 1. A clinicopathologic study of 19 mesodermal mixed tumors. Surg Gynec Obstet 100: 232-242, Feb 1955

10. Krupp PJ Jr, Sternberg WH, Clark WH, et al: Malignant mixed Müllerian neoplasms (mixed mesodermal tumors). Am J Obstet Gynecol 81:959-969, May 1961

11. Edwards DL, Sterling LN, Keller RH, et al: Mixed heterologous mesenchymal sarcomas (mixed mesodermal sarcomas) of the uterus. Addition of 7 cases. Am J Obstet Gynecol 85:1002-1011, Apr 15, 1963

12. Falkinburg LW, Hoey WO, Savran J, et al: Mesodermal mixed tumor of the corpus uteri—Review and report of six cases, one of which has survived fifteen years. Am J Obstet Gynecol 90: 450-459, Oct 15, 1964

13. Mortel R, Nedwich A, Lewis GC Jr, et al: Malignant mixed müllerian tumors of the uterine corpus. Obstet Gynecol 35:468-480, Mar 1970

14. Speert H, Peightal TC: Malignant tumors of the uterine fundus subsequent to irradiation for benign pelvic conditions. Am J Obstet Gynecol 57:261-273, Feb 1949

15. McElin TW, Davis H Jr: Mesodermal mixed tumor of the corpus uteri. Am J Obstet Gynecol 63:605-612, Mar 1952

16. Schiffer MA, Mackles A, Wolfe SA: Reappraisal of the diagnosis in uterine sarcoma—Review of forty-nine cases. Am J Obstet Gynecol 70:521-539, Sep 1955

17. Taylor CW: Mesodermal mixed tumours of the female genital tract. J Obstet Gynecol Brit Emp 65:177-188, Apr 1958

18. Ober WB, Tovell HMM: Mesenchymal sarcomas of the uterus. Am J Obstet Gynecol 77:246-268, Feb 1959

19. Ricciutti V, Noble AJ, Kiefer L: Malignant mixed mesodermal tumor of the uterus—Report of a case. Obstet Gynecol 18:757-762, Dec 1961

20. Heinrichs WL, Climie ARW, Cook JC: Cure of primary mesodermal mixed tumor by radiotherapy. Obstet Gynecol 19:537-541, Apr 1962

21. Rachmaninoff N, Climie ARW: Mixed mesodermal tumors of the uterus. Cancer 19:1705-1710, Nov 1966

22. Chaves E: Malignant mesodermal mixed tumors of the uterus—Report of 3 cases one of which associated with squamous cell carcinoma of the cervix and schistosomiasis of the uterine wall. Am J Obstet Gynecol 96:1017-1021, Dec 1, 1966

23. Norris HJ, Roth E, Taylor HB: Mesenchymal tumors of the uterus—II. A clinical and pathologic study of 31 mixed mesodermal tumors. Obstet Gynecol 28:57-63, Jul 1966

24. Mendel EB, Lucas WF, Panopio I: Malignant mixed mullerian tumors of the uterus. Obstet Gynecol 30:66-69, Jul 1967

25. Persaud V, Knight LP: Malignant mesenchymal tumours of the corpus uteri. West Indian Med J 17:96-102, Jun 1968

26. Gudgeon DH: Mixed mesodermal tumour of the uterus occurring after radiotherapy. Proc Roy Soc Med 61:1281, Dec 12, 1968

27. Ruffolo EH, Metts NB, Sanders HL: Malignant mixed mullerian tumors of the uterus—A clinicopathologic study of 9 patients. Obstet Gynecol 33:544-552, Apr 1969

28. Masterson JG, Kremper J: Mixed mesodermal tumors. Am J Obstet Gynecol 104:693-698, Jul 1, 1969

29. Edwards CL: Undifferentiated tumors, *In* Cancer of the Uterus and Ovary. 11th Clinical Conference on Cancer, M. D. Anderson Hospital and Tumor Institute, Houston, Texas. Chicago, Year Book Medical Publishers Inc, 1969. pp 84-94

30. Glover JB: Mixed mesodermal tumors—Report of a case. North Carolina Med J 31:461-462, Dec 1970

31. Reddy DJ, Bharma T, Sankaran V, et al: Corporeal mesodermal mixed tumours of the uterus. J Indian Med Ass 54:153-157, Feb 16, 1970

32. Schaepman-Van Guens EJ: Mixed tumors and carcinosarcomas of the uterus evaluated five years after treatment. Cancer 25:72-77, Jan 1970

33. Giarratano RC, Slate TA: Sarcomas of the uterus. Obstet Gynecol 38:472-477, Sep 1971

34. Czernobilsky B, Labarre GC: Carcinosarcoma and mixed mesodermal tumor of the ovary—A clinicopathologic analysis of 9 cases. Obstet Gynecol 31:21-32, Jan 1968

35. Saunders P, Price AB, Taylor RW: Mixed mesodermal tumour of the ovary arising in pelvic endometriosis. Proc Roy Soc Med 63:1050-1051, Oct 1970

36. Sternberg WH, Clark WH, Smith RC: Malignant mixed müllerian tumor (mixed mesodermal tumor of the uterus). Cancer 7:704-724, Jul 1954

37. Aaro LA, Symmonds RE, Dockerty MB: Sarcoma of the uterus—A clinical and pathologic study of 177 cases. Am J Obstet Gynec 94:101-109, Jan 1, 1966

38. Hill RP, Miller FN Jr: Combined mesenchymal sarcoma and carcinoma (carcinosarcoma) of the uterus. Cancer 4:803-816, Jul 1951

39. Marcella LC, Cromer JK: Mixed mesodermal tumors—A report of 11 cases. Am J Obstet Gynecol 77:275-285, Feb 1959

40. Rubin A: The histogenesis of carcinosarcoma (mixed mesodermal tumor) of the uterus as revealed by tissue culture studies. Am J Obstet Gynecol 77:269-274, Feb 1959

41. Lebowich RJ, Ehrlich HE: Mesodermal mixed tumors of corpus uteri—Report of a case with review of the literature. Surgery 10:411-433, Sep 1941

42. Murray MR: Cultural characteristics of three granular-cell myoblastomas. Cancer 4:857-865, Jul 1951

43. Pogogeff IA, Murray MR: Form and behavior of adult mammalian skeletal muscle in vitro. Anat Rec 95:321-335, May 1946

44. Williams TJ, Woodruff JD: Similarities in malignant mixed mesenchymal tumors of the endometrium. Obstet Gynecol Surv 17:1-18, Feb 1962

45. Carter ER, McDonald JR: Uterine mesodermal mixed tumors. Am J Obstet Gynecol 80:368-373, Aug 1960

46. Vellios F, Stander RW, Huber CP: Carcinosarcoma (malignant mixed mesodermal tumor) of the uterus. Am J Clin Path 39:496-505, May 1963

47. Glass M, Goldsmith JW Jr: A review of 94 mixed mesodermal tumors of the uterus, with a report of an additional case. Am J Obstet Gynecol 41:309-317, Feb 1941

Management of the Acute and Subacute Phases of Alcohol Abuse: Taking a Drinking History

The technique of taking a drinking history is a technique that you can develop. The technique is not, "Do you drink?", "How much do you drink?", "How often do you drink?" and "How long have you been drinking?" Those are all the wrong questions to ask. They're judgmental on the front end. You will never get a truthful answer . . . never.

There are some guidelines to taking a drinking history: First, you might as well assume that 70 percent of your adult population drink on somewhat more than a casual basis. You should begin to initiate the conversation by discussing the patient's *use* of alcohol, not his *abuse*. And the questions of "how much" and "how long" imply abuse on the front end.

You must convince the patient that alcohol is a drug, and he is self-prescribing the drug for the effect. Ask him about the effect he's looking for. Does he have the same effect every time he drinks? Is it taking a little bit more alcohol now? What is the social setting in which he takes alcohol? What is the relationship of alcohol to meals? And without asking him directly, how much, how often, how long, he will tell you. And if you can get a patient to tell you without asking him, then you have become a good drinking historian. Be as non-judgmental and non-moralistic as possible in taking the history; and the whole point of taking the history is to find out how important alcohol is to this individual . . . Begin to appreciate that alcohol is indeed involved probably in a lot more medical disorders than you have previously suspected . . . You occupy a very critical position in directing the health care of this individual if indeed he is addicted to alcohol and if indeed he needs more help than this. So the physician really does stand at a unique vantage point in making an early diagnosis and intervening early in a treatment situation. And if we do this, then we are operating at the best secondary level of preventive medicine. That's early intervention and early treatment. And if we do this, then I think we will indeed make an impact on the public health problem that's going to get a lot worse before it gets any better.

—David H. Knott, MD, *Memphis*

Extracted from *Audio-Digest Internal Medicine,* Vol. 20, No. 4, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Refer to: Lewin AJ: Acupuncture and its role in modern medicine. West J Med 120:27-32, Jan 1974

Acupuncture and Its Role in Modern Medicine

ANDREW J. LEWIN, MD, *Los Angeles*

Although both the philosophic and physiologic basis of acupuncture seems fanciful to Western medical thinking, the results obtained in the treatment of certain disease states cannot be lightly dismissed. Its use in the induction of surgical analgesia may have immediate application for Western Medicine.

Its mechanism of action is a complete enigma, but information accumulated from research in hypnosis, visceral learning and, most important, the physiology of pain perception may contain clues to the pathophysiologic principles involved.

The fact that many disorders for which acupuncture therapy is useful are thought to have a large psychosomatic component only serves to reinforce the Eastern concept of inseparability of mind and body. A great deal of attention is being given to this concept in the current medical literature.

In order to define the role of acupuncture in modern medical practice, a more scientific approach in both clinical and basic research is necessary. If acupuncture can be proved safe and efficacious in the treatment of certain diseases, lack of knowledge regarding its mechanism of action should not delay its incorporation into our medical armamentarium.

ACUPUNCTURE IS ONE of the world's oldest healing arts. It encompasses an empiric body of knowledge accumulated over the past five thousand years. So little scientific information has appeared in the literature that an accurate appraisal of the therapeutic value of acupuncture is difficult. Moreover, ancient and modern approaches to acupuncture, although very different, are often confused, making interpretation of results impossible.

The ancient Chinese concept of disease and its schema for acupuncture therapy were thoroughly covered in a recent review,[1] therefore this paper will concentrate on acupuncture as it is practiced today and on some of the possible physiologic mechanisms involved.

From the Cedars-Sinai Medical Center, Los Angeles, and the Department of Medicine, University of California, Los Angeles, Center for the Health Sciences.

Submitted March 6, 1973.

Reprint requests to: A. J. Lewin, MD, Cedars-Sinai Medical Center, Mount Sinai Hospital Division, Box 48750, Los Angeles, CA 90048.

Modern Acupuncture

The modern practice of acupuncture, although superficially resembling the acupuncture practiced in ancient China, is actually quite different. The schema of the meridians is retained because of its utility in learning the acupuncture points. However, ancient explanations for the mechanisms of action have largely been abandoned. A distinction is drawn between those procedures which have a direct bearing on therapeutic results and other practices which are the result of religious and philosophic beliefs. For example, the use of gold or silver needles to achieve the differing therapeutic results of tonification or sedation has been abandoned. Acupuncture is now done with stainless steel needles, since it was recognized that the important factor was pricking of the skin rather than the composition of the needle.

Similarly, the use of pulse diagnosis is no longer a prerequisite for acupuncture treatment. Although it is still used in the Orient and by some Western practitioners, modern acupuncturists with a background of medical training use sophisticated diagnostic techniques before acupuncture treatment is given. This is true in the major medical centers of mainland China where acupuncture is used extensively.

The number and location of acupuncture points used by modern practitioners has changed since ancient times. The "barefoot doctors" of mainland China provide complete care to a large population of rural Chinese, using only about 50 different acupuncture points. Most of these are the very potent points handed down for many generations. Others have been recently discovered, primarily through two different methods. The first is by the clinical observation of therapeutic results while pricking in new locations. The second evolves from the discovery that the electrical conductance at acupuncture points is different from that at other places in the skin. New acupuncture points were found by looking for places of high electrical conductivity using a Wheatstone bridge apparatus capable of measuring small voltage differences.[2]

Although the practice of acupuncture has recently received a great deal of publicity in the United States, largely due to reports by Americans who visited mainland China,[3-6] it has actually been practiced in this country for many years both by physicians and by non-medically trained acupuncturists, and there are isolated reports of its efficacy in the medical literature of the last century.[7,8]

Two therapeutic modes of acupuncture are used in practice today: (1) acupuncture used for the treatment of many diseases and (2) acupuncture employed as an anesthetic procedure (a more accurate term for this would be surgical analgesia).

Almost every conceivable affliction of mankind has been reported at one time or another to be treatable by acupuncture.[1,9-11] Besides its more widely known use in various chronic pain syndromes, such as causalgia, renal and biliary colic, dysmenorrhea, sciatica and glaucoma, some of the specific disorders which are reported to respond well to acupuncture therapy include allergic diseases, such as asthma, hayfever, rhinitis[12] and eczema; muscular skeletal disorders, such as arthritis, gout and neuralgia; gastrointestinal diseases, such as peptic ulcer, diarrhea, constipation and colitis; neurologic disorders, such as paralysis secondary to poliomyelitis[13] and nerve deafness;[14] infectious diseases[15] including epidemic encephalitis and liver abscess; surgical diseases, including acute abdominal conditions and severe hemorrhage[6] and mental illness. Acupuncture therapy is the treatment of choice for acute appendicitis in many Oriental countries.[16]

It is impossible, however, to assess the validity of these accounts, since the type of scientific documentation that forms the basis for Western medical knowledge is almost totally lacking in these completely uncontrolled and often anecdotal reports. Most practitioners agree, however, that once structural changes have taken place, acupuncture is no longer very useful.

With our present degree of knowledge of acupuncture, these reports cannot be totally dismissed. But, to be taken seriously by Western physicians, more careful studies are necessary.

The newest and probably the most dramatic clinical application of acupuncture is as an anesthetic agent. It is this use of acupuncture more than any other which has stimulated the interest of Western observers.[6,17,18] Acupuncture anesthesia was first used in mainland China in 1958 and was immediately recognized to have numerous advantages. Since then its use has been increasing rapidly. It has been used in approximately 50,000 major surgical operations in Peking alone.[19]

Acupuncture anesthesia has been used in almost every type of surgical procedure, including thoracotomy and lobectomy, subtotal gastrectomy, lobotomy for excision of brain tumor, oophorectomy, cesarean section, dental operations

and ophthalmic procedures. In many cases acupuncture alone is used; in others small doses of analgesics, narcotics or sedatives are used in conjunction with the acupuncture. The reported success rate ranges between 75 and 99 percent, varying with the type of surgical procedure rather than any classification of patients. But there is also careful preoperative selection and training of the patients, which is not well detailed in the reports and certainly biases the statistics. Although still successful in a majority of cases, acupuncture anesthesia was found to be less useful in abdominal procedures where satisfactory muscle relaxation is difficult to achieve and traction on the viscera often produces some discomfort.

The details of needle placement and other procedures involved in acupuncture anesthesia are not within the scope of this discussion. Suffice it to say that anywhere from one to a dozen needles are used, their placement dictated by reference to acupuncture charts and clinical experience. Another technique commonly employed is the attachment of an electric generator to the acupuncture needles after they are placed.[20] Stimulation with an alternating current is then applied during the course of the surgical procedure. In other procedures, needles are manipulated manually by the anesthetist.

Besides the obvious avoidance of toxic reactions to the anesthetic agent itself, there are many other advantages to anesthesia of this type. Since a large proportion of surgical morbidity and mortality is due to complications of anesthesia rather than to the procedures themselves, any technique which could decrease these untoward effects would have a significant impact on the outcome of many operations. "Poor risk" surgical patients should be especially benefited. The patients are never unconscious and, therefore, the dangers inherent in supporting cardiac, respiratory and renal function are diminished. The concern about vital system function in the fetus during cesarean section or any other surgical procedure in pregnant women would be similarly lessened.

Postoperative recovery is more rapid since there is no need for recovery from the anesthetic agent. The analgesic effects of acupuncture persist for several hours after operation, and beyond that repeated needling of the same points is frequently employed for the treatment of postoperative pain.

Under acupuncture anesthesia the patient is able to communicate with the operating surgeon. The importance of this should not be underestimated, for in many instances a cooperative patient can significantly decrease the surgical morbidity and increase the chances for surgical success. For example, in operations for ocular muscle weakness, instead of hopefully guessing where paralyzed muscles should be transplanted, the surgeon could more accurately align the eye because the patient is awake and able to cooperate with him in testing his extra-ocular movements. Another example would be thyroid gland operations, in which the danger of damage to the recurrent laryngeal nerve could be lessened by asking the patient to move his vocal cords.

Possible Pathophysiologic Mechanisms Involved in Acupuncture

There are numerous theories concerning the way in which acupuncture produces its effects. Many of these are based on ancient religious and philosophic beliefs and will not be further discussed here. It must be remembered, however, that in the eyes of many practitioners these religious and philosophic explanations are more "logical" and "rational" than the modern scientific theories that Western medical science proposes, for data accepted as "proof" in different cultures are very much related to their fundamental concepts of nature and life.

In general, acupuncture practitioners believe that the acupuncture points are in some way related to the autonomic nervous system, while many Western trained physicians believe that all of the results obtained through acupuncture can be explained by hypnosis, autosuggestion or a placebo effect. Many of the techniques used in hypnosis are also used during acupuncture therapy, but these same techniques also play a role in most other types of therapeutic endeavors.

One of the most important elements for successful hypnosis is the ability of the hypnotist to obtain compliance from the patient.[21] The primary objective is to manipulate the patient's internal and external environment, so he will be more receptive to suggestions. There are many methods used to induce compliance. It may be done entirely verbally; it may employ physical contact and manipulation; and it may even involve the use of gadgets, devices or machines to capture the attention of the subject.

It is easy to see how the aura surrounding acupuncture lends itself to the creation of compliance and suggestibility in the patient.[22] Treatment for many and divers conditions is usually initiated by

the placement of acupuncture needles in the first finger web between the thumb and index finger of each hand. This pricking of the "Ho Ku" point, a very powerful acupuncture point, results in a feeling of soreness, tingling, heaviness or distension throughout the hand and sometimes throughout the entire forearm. This may very well place the patient in the desired state of suggestibility so that further pricking of acupuncture points for the treatment of a specific condition is done after the patient is convinced of the ability of acupuncture to produce widespread effects and thus disposed to a positive therapeutic result.[23,24] In circumstances more familiar to us in this country, similar conditions are established with the taking of vital signs by the nurse when a patient first enters the physician's office; with the use of the stethoscope to auscultate the heart and lungs; or with the prescription of analgesics to treat pain syndromes.

One possible clue to the mechanism of action of acupuncture is found in the research on visceral learning conducted during the past several years.[25-28] It is now evident that autonomic functions such as heart rate maintenance, blood pressure control and core temperature regulation can be rather easily learned by both laboratory animals and man under the appropriate experimental conditions. Yogic practices probably utilize similar autonomic training.[29,30]

It is beyond the scope of this paper to discuss the important implications that this holds for current pathophysiologic interpretations in all aspects of medicine, but it may help to explain how diseases, felt to be purely organic in origin, may be successfully treated by acupuncture. Perhaps the peripheral stimulation of the acupuncture needles acts in some way as a stimulus for retraining visceral responses to function more normally and thus "cure" the underlying disease process. This, of course, is a highly speculative concept and would require a great deal of experimental work for validation.

Acupuncturists refute the role of hypnosis in their therapy by claiming that acupuncture can be used in unwilling and unbelieving patients; that it is effective in unconscious patients (needling comatose accident victims has reportedly instantaneously stopped severe hemorrhage); that it can be used very effectively in the treatment of young children;[31] and that it can be used in animal experiments[32] (after being anesthetized with acupuncture, a mule was eviscerated through an abdominal incision without any evidence of pain perception).

Many Asian countries and the USSR are actively engaged in research on the possible mechanisms through which acupuncture achieves its effects. Although it is very difficult to determine the scientific validity of these experiments, some of the reported findings are of interest.

By using an electrical probe, acupuncture points have been found to have a greater positive charge than the surrounding tissue.[33] Stimulation of one acupuncture point has caused changes in the electrical conduction at distant acupuncture points along the same meridian. If the meridian is transected, these changes in conduction do not occur.

Using myelin stains, a cluster of nerve cells in the pinna of the ear has been located.[6] Stimulation of these cells produces changes in the electrical resistance of the skin over the abdomen. This may explain why the needling of the pinna produces anesthesia sufficient for abdominal operations.

A Korean biologist, Kim Bong Han, discovered small oval cells allegedly not found elsewhere, subepidermally at acupuncture points.[2] He has also located anatomic structures connecting acupuncture points which are histologically different from blood vessels, lymphatics and nerves and do not contain cellular elements. Supposedly, transection of these structures prevented electrical conduction to other acupuncture points and to internal organs. It must be restated that the specific techniques and actual data from which these conclusions are drawn are unavailable in the literature. Many of the results are probably due to technologic errors rather than actual mechanisms responsible for acupuncture's effects (the findings of Kim Bong Han are probably the result of artifacts produced by the fixation and staining of the tissue).

Is there other available experimental work, then, that is scientifically valid and that might shed some further light on the pathophysiologic mechanisms? In 1965 Melzack and Wall proposed a new theory of pain transmission and pain perception.[34] Basically, their *gate control* theory stresses the importance of the spinal cord (specifically the substantia gelatinosa) in modulating both the intensity and frequency with which peripheral nerve impulses are transmitted to the perceptual centers of the brain.

The substantia gelatinosa consists of small densely packed cells that form a functional unit extending the length of the spinal cord; the cells

connect with one another by short fibers and by the longer fibers of Lissauer's tract. The gate control theory proposes that the large nerves ("A" fibers) which enter the spinal cord not only stimulate the firing of the first central transmission cells (T-cells) which cause transmission to the perceptual centers, but also stimulate the cells of the substantia gelatinosa, which in turn act to inhibit firing of the T-cells. The small nerves ("C" fibers), on the other hand, not only stimulate T-cell transmission, but also have the effect of inhibiting the firing of the cells of the substantia gelatinosa and thereby enhance T-cell transmission.[35]

This theory explains very nicely how perception of peripheral stimulation, such as pain, temperature and distension, may be greatly influenced by other peripheral stimulations even at quite distant and apparently unrelated locations. The literature contains many references to the induction of altered perception of peripheral events by the use of different stimuli. Itching can be decidedly reduced by the application of vibration to the itching area.[36,37] It can also be reduced by application of vibrating stimulation to distant areas. Vibration can also increase the threshold for the perception of an electric shock. This effect lasts a long time after the vibration has ceased.[38]

The relief of phantom limb pain that some amputees obtain by gently tapping the stump with a rubber mallet, whereas heavier pressure increases the intensity of the pain,[39] may also be explained by postulating that differential stimulation of the "A" and "C" fibers occurs. The implantation of electrical stimulators directly in the spinal cord to relieve severe symptoms in certain patients with chronic pain syndromes is a direct application of this theory.[40]

Application of the gate control theory and other experimental work to acupuncture therapy would lead one to conclude that needling is probably not necessary to achieve the results. Stimulation of other sensations in the periphery should be capable of producing beneficial effects. The effect of moxibustion, the combustion of an herb directly on the skin or wrapped around an acupuncture needle, could then be explained by the stimulation of pain and temperature perception. Japanese finger pressure therapy (shiatsu) utilizes firm pressure over certain areas to treat many diseases.[41] This, too, could be explained by the gate control theory.

Perception of visceral sensations may also be modulated by the gate control mechanism in the substantia gelatinosa. Cardiac pain has been reported to be abolished by the injection of a local anesthetic in trigger areas on the chest wall.[42] By applying thermal, mechanical and chemical stimulation to the skin of the abdomen and back, circulatory changes in the small vessels of the intestines can be induced.[43-45] Reports in the acupuncture literature, although difficult to validate, seem to relate very similar findings. Intraluminal pressure recordings of the stomach have shown that when the point of tonification of the stomach meridian is stimulated, peristaltic contractions increase. Conversely, by electrically stimulating the gastric mucosa, changes in conduction at acupuncture points along the stomach meridian were found.[2,46]

With the use of an electrical probe in the cerebral cortex of cats, recordings could be obtained when painful stimuli were applied in the periphery. By needling the appropriate acupuncture points the voltage change in the cortex was reduced.[6] In the medical literature there is a report of a patient with an old parietal lobe lesion who perceived circumscribed pain and temperature sensations in the absence of apparent external stimulation.[47] These sensations could be inhibited by superficial pressure, vibration or touch applied to other anatomic areas.

The actual mechanism of action of acupuncture is probably a combination of both psychologic and physiologic events. This, of course, would be very similar to the way in which other therapeutic modalities act. It is only the relative importance of the two mechanisms that remains to be clarified.

Precautions

A brief mention of the potential problems resulting from acupuncture therapy should be made because, as with any other therapeutic procedure, complications can occur.

Probably the most important of all problems involving acupuncture is its use in place of Western medical therapy. Physicians and acupuncture practitioners should be circumspect and conservative in their appraisal of what acupuncture can accomplish. Western medicine has developed many diagnostic and therapeutic techniques which have proved efficacious after many years of study and experience. Where it is employed, acupuncture should be used as an adjunctive form of therapy to standard medical treatment, not as a replacement for conventional cures.

There is the possibility that patients would seek standard medical treatment only after acupuncture

had failed to produce results. The literature contains very little information about this hazard, although the military medical literature from Vietnam contains reports of such cases among the Vietnamese population.[48] Often complications arise which could have been averted if early diagnosis and prompt treatment with Western techniques had been instituted.

Some of the hazards, such as hepatitis and local infection from improperly sterilized needles, are quite obvious. Only their frequency and severity remain to be documented. The incidence of these complications can be drastically reduced if modern techniques of sterilization and antisepsis are employed. Bleeding from the puncture of large blood vessels may also occur, but the needles are so small that this does not present a major hazard.

Occasionally a needle may break off in the patient and remain as a foreign body. Eventually most of these will work their way to the surface and be extruded. However, it is possible for these fragments to reach deeper locations and to penetrate other organs. Since some acupuncture points are in close proximity to joint spaces, some are within the joints themselves and some are in close proximity to large nerves, the effects of repeated needling and the possible foreign body reaction in these areas must be closely examined.

REFERENCES

1. Veith I: Acupuncture in traditional Chinese Medicine—An historical review. Calif Med 118:70, Feb 1973
2. Mann F: Acupuncture, 2nd Ed. London, W. Heinemann Medical Books, Ltd., 1971
3. Reston J: New York Times. Jul 26, 1971, and Aug 22, 1971
4. Snow E: New Republic, May 1, 1971, p 20
5. Dimond EG: Saturday Review. 54:15-17, 71, 1971
6. Dimond EG: Acupuncture anesthesia—Western medicine and Chinese traditional medicine. JAMA 218:1558, 1971
7. Manaley T: On the local abstraction of blood in the arthrosis of the extremities. JAMA 29:773, 1897
8. Lee WM: Acupuncture as a remedy for rheumatism. South Med Surg J 1:129, Aug 1836
9. Mann F: The Treatment of Disease by Acupuncture. London, W. Heinemann Medical Books, Ltd., 1967
10. Moss L: Acupuncture and You. London, Elek Books, 1964
11. Veith I: Acupuncture therapy—Past and present. JAMA 180:478, 1962
12. Lembong JT: A new approach to the problem of allergic nasal disorders. Paediat Indonesiana 10:239, 1970
13. Jen Sheu-Chung: Acupuncture in the treatment of paralytic poliomyelitis. Paediat Indonesiana 5:Suppl 699-702, 1965
14. Be red vanguards to implement Chairman Mao's revolutionary medical and health line. China's Med 3:339, 1968
15. Korobkov ES, Leontiev FL: Precious medical heritage. China Reconstructs. Mar 1958, p 20
16. Lu Wei-Po, Yu Yung-Ching: Learning from ancient China's medicine. China Reconstructs. Oct 1959, p 32
17. Capperauld I, Cooper E, Saltoun D: Acupuncture anesthesia in China. Lancet, Nov 1972, p 1136
18. Capperauld I: Acupuncture anesthesia and medicine in China today. Surg Gyn Obs 135:440, 1972
19. Shute WB: East meets West (1): Canadian eyes peek across the acupuncture threshold. Canad Med Ass J 107:1002, 1972
20. Urquhart IA: Drugless anesthesia by acupuncture. Ariz Med 29:575, 1972
21. Gordon JE (Ed): Handbook of Clinical and Experimental Hypnosis. New York, The Macmillan Co., 1967
22. Wolffenbuttel E: Hypnosis and acupuncture, XIII (concluded). Rev Brasil Med 25:827, 1968
23. Paul GL: Physiological effects of relaxation training and hypnotic suggestion. J Abnorm Psychol 74:425, 1969
24. Grim PF: Psychotherapy by somatic alteration. Ment Hyg 53:451, 1969
25. DiCara LV: Instrumental learning of visceral and glandular responses and implications for psychosomatic medicine. Proc 76th Ann Conven Am Psychol Ass, 1968, p 259
26. Green EE, Green AM, Walters ED: Self-regulation of internal states. Proc Internatl Cong Cybernet, London, 1972
27. Jacobson E: Neuromuscular controls in man: methods of self direction in health and disease. Am J Psychol 68:549, 1955
28. Miller NE: Learning of visceral and glandular responses. Science 163:434, Jan 1969
29. Bagchi BK, Wenger MA: Electro-physiological correlates of some Yogi exercises. Electroenceph Clin Neurophysiol Suppl 7: 132, 1957
30. Wenger MA, Bagchi BK: Studies of autonomic functions in practitioners of yoga in India. Behav Sci 6:312, 1961
31. Research Institute of Acupuncture and Moxibustion, Academy of Traditional Chinese Medicine. Foreign Language Press, Peking, 1960. Reported in Far East Reporter, M. Russell, ed. Mar 1972
32. New Chinese News Agency, Oct 18, 1971
33. Niboyet JEH: Etude sur la moindre resistance cutanee a l'electricite des certains points de la peau dits "points Chinois." Bull de la Soc d'Acupuncture 39:16, 19-88, 1st trimester, 1961
34. Melzack R, Wall PD: Pain mechanisms—A new theory. Science 150:971, 1965
35. Melzack R, Wall PD: Psychophysiology of pain. Int Anesthes Clin 8:3, 1970
36. Wall PD, Cronley-Dillon JR: Pain, itch and vibration. AMA Arch Neurol 2:365, 1960
37. Melzack R, Schecter B: Itch and vibration. Science 147: 1047, 1965
38. Melzack R, Wall PD: Masking and metacontrast phenomena in the skin sensory system. Exper Neurol 8:35, 1963
39. Livingston WK: Pain Mechanisms. New York, The Macmillan Co., 1943
40. Wall PD, Sweet WH: Temporary abolition of pain in man. Science 155:108, 1967
41. Namikoshi T: Japanese finger-pressure therapy—Shiatsu. Tokyo, Japan Publications, Inc., 1972
42. Travell J, Rinzler SH: Relief of cardiac pain by local block of somatic trigger areas. Proc Soc Exper Biol Med 63:480, 1946
43. Kuntz A, Haselwood LA: Circulatory reactions in the gastrointestinal tract elicited by localized cutaneous stimulation. Am Heart J 20:743, 1940
44. Kuntz A: Anatomic and physiologic properties of cutaneovisceral vasomotor reflex arcs. J Neurophysiol 8:421,1945
45. Richins CA, Brizzee K: Effect of localized cutaneous stimulation on circulation in duodenal arterioles and capillary beds. J Neurophysiol 12:131, 1949
46. Deutsche Zeitschrift fur Akupunktur. Band VI, Heft 1-2, 1958
47. Trent SET: Peripheral sensory inhibition of pain with a parietal lobe lesion. J Nerv Ment Dis 123:356, 1956
48. Rich NM, Dimond FC: Results of Vietnamese acupuncture seen at the second surgical hospital. Military Med 791, Oct 1967

Medical
PROGRESS

Refer to: Mercer PF, Maddox DA, Brenner BM: Current concepts of sodium chloride and water transport by the mammalian nephron (Medical Progress). West J Med 120:33-45, Jan 1974

Current Concepts of Sodium Chloride and Water Transport by the Mammalian Nephron

PAUL F. MERCER, PhD, *London, Ontario*
DAVID A. MADDOX, PhD, *and* BARRY M. BRENNER, MD, *San Francisco*

FOREWORD

The decision of the editors to solicit a review for the Medical Progress series of this journal devoted to current concepts of the renal handling of salt and water is sound in that this important topic in kidney physiology has recently been the object of a number of new, exciting and, in some instances, quite unexpected insights into the mechanisms governing sodium excretion. These developments have come about largely as a consequence of the fact that segments of nephrons previously inaccessible to direct study are now readily accessible.

Many of the findings to be discussed argue for extensive revision of a number of our current widely held views concerning the renal handling of sodium chloride and water. In the opinion of the authors, the strength of this argument rests in the fact that many of these new findings were obtained under circumstances that enabled workers to gain more direct access to the nephron than has been possible heretofore. This is not to say that areas of controversy and disagreement no longer exist. Wherever possible, these have been identified. In attempting to provide a comprehensive review of this topic, it has been necessary at times to overgeneralize and to disregard minor deficiencies in some of the studies cited. Finally, we wish to emphasize that a considerable portion of the information contained herein derives from work still under active investigation. Much of this contemporary work will undoubtedly withstand the rigors of future experimental scrutiny. It is inevitable, however, as William James so aptly noted in the quotation cited below, that some of our present ideas will need to be abandoned or revised in favor of newer, more convincing evidence. Seen in this light, the present effort is intended as nothing more than a timely survey of this active and fertile topic in renal physiology.

From the Departments of Medicine, Veterans Administration Hospital, San Francisco, and the University of California, San Francisco. (Dr. Mercer's permanent address is Department of Physiology, University of Western Ontario, Faculty of Medicine, London, Ontario, Canada).

Reprint requests to: B. M. Brenner, MD, Veterans Administration Hospital, 4150 Clement Street, San Francisco, CA 94121.

Science like life feeds on its own decay. New facts burn old rules; then newly developed concepts bind old and new together into a reconciling law.

—WILLIAM JAMES

Glomerulus

A. N. Richards and associates[1,2] and Walker[3] provided experimental verification of Carl Ludwig's more than century-old hypothesis[4] that the initial step in the process of urine formation involves the elaboration of a nearly ideal ultrafiltrate of plasma across the walls of the glomerular capillaries. These studies, demonstrating that the fluid in Bowman's space has essentially the same composition as plasma with respect to water and low molecular weight solutes, were confined to frogs and necturi, species of amphibia in which glomeruli and surrounding Bowman's capsules are readily accessible to micropuncture. Few such direct measurements of the composition of fluid in Bowman's space have been performed in the mammalian kidney owing to the infrequent presence of glomeruli as surface structures in the mammal. On those rare occasions, however, when surface glomeruli were encountered in rat, guinea pig, and oppossum, Walker, Bott, Oliver, and MacDowell[5] were successful in establishing that, for these species as well, the composition of fluid transported across the glomerular capillary conforms closely to that of an ideal ultrafiltrate.

Ludwig's contribution to our understanding of glomerular function derives not only from his prediction that the fluid in Bowman's space has the characteristics of a nearly ideal ultrafiltrate, but extends also to a qualitative description of the transcapillary forces responsible for the formation of this ultrafiltrate.[4] Thus, in suggesting that glomerular capillary hydrostatic pressure normally exceeds the sum of the opposing pressures (which he viewed as being determined primarily by what has come to be known as the colloid osmotic pressure of the capillary blood), Ludwig laid the basis for the more quantitative formation by Starling[6,7] that the magnitude and direction of fluid movement across a capillary wall is governed largely by the algebraic sum of the transcapillary hydrostatic and colloid osmotic pressure differences. Stated in terms of this familiar Starling relationship, the rate of formation of ultrafiltrate across capillary walls of a single glomerulus is given by the expression:

$$\text{SNGFR} = K_f[(\overline{P}_{GC} - P_T) - (\overline{\pi}_{GC} - \pi_T)]^*$$

where SNGFR is the single nephron glomerular filtration rate, K_f, the ultrafiltration coefficient, $\overline{P}_{GC}$ and P_T, mean glomerular capillary and proximal tubule hydrostatic pressures, and $\overline{\pi}_{GC}$ and π_T, the corresponding colloid osmotic pressures. Whereas a proportional relationship between ultrafiltration rate and net transcapillary driving force has been demonstrated experimentally for capillaries in the mesentery, omentum, and skeletal muscles of a number of amphibian and mammalian species,[8-11] direct evidence in support of a similar relationship for glomerular capillaries has been confined, until recently, only to amphibia.[12,13]

In the past few years, however, an important discovery and a series of technological advances have enabled workers to acquire similarly direct evidence in the mammalian kidney.[14] Principal among these has been the discovery in the laboratory of Dr. Klaus Thurau of the Physiological Institute, Munich, of a unique strain of Wistar rats endowed with glomeruli situated on the renal cortical surface.[14] Using these rats, Brenner, Troy, and Daugharty[14] found mean glomerular capillary hydrostatic pressure ($\overline{P}_{GC}$) to average approximately 45 mm of mercury, or some 40 percent of the mean aortic pressure. It is important to note that the value of 45 mm of mercury for $\overline{P}_{GC}$ obtained with these direct methods is considerably lower than that generally estimated for the rat using indirect techniques such as single nephron stop-flow or ureteral occlusion.[15-17] An explanation for this disparity between direct and stop-flow measurements is provided by the recent finding that the hydrostatic pressure in single capillaries of accessible glomeruli tends to increase, often substantially, when the flow of tubule fluid is stopped.[18] The higher pressures during stop-flow are probably the consequence of compensatory vasodilation of the afferent arteriole in response to elevations in proximal tubule pressure induced by stop-flow.

The lower values of $\overline{P}_{GC}$ obtained by direct measurement indicate that the net driving force for ultrafiltration is also considerably lower than previously thought. Chart 1 summarizes the net

*This equation is referred to elsewhere in this article as Equation 1.

GLOMERULAR CAPILLARY HYDROSTATIC AND ONCOTIC PRESSURES
(mm Hg)

	Afferent End	Efferent End
P_{GC}	45	45
P_T	10	10
π_{GC}	20	35
$P_{UF} = P_{GC} - P_T - \pi_{GC}$	15	0

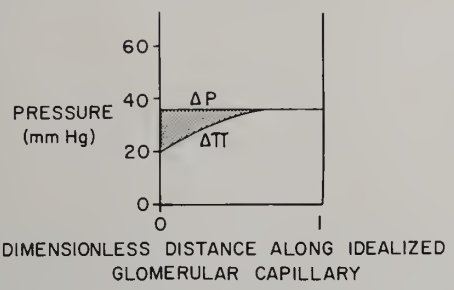


Chart 1.—Hydrostatic and colloid osmotic pressure profiles along an idealized glomerular capillary. $\Delta P = P_{GC} - P_T$ and $\Delta\pi = \pi_{GC} - \pi_T$, where P_{GC} and P_T are the hydrostatic pressures in the glomerular capillary and Bowman's space, respectively, and π_{GC} and π_T the corresponding colloid osmotic pressures.

pressures inferred from these direct measurements. Here the abscissa represents the normalized distance along an idealized glomerular capillary, zero being the afferent end and 1 the efferent end. The local value of glomerular capillary hydrostatic pressure (P_{GC}) is inferred to be the same at afferent and efferent ends of the capillary, about 45 mm of mercury, and P_T, the opposing proximal tubule pressure, is about 10 mm of mercury. ΔP, the difference between P_{GC} and P_T, or 35 mm of mercury, is therefore essentially constant along the length of the capillary, in accord with experimental findings.[14,19] Measurements of afferent and efferent arteriolar plasma protein concentrations indicate that the colloid osmotic pressure, π_{GC}, increases from about 20 mm of mercury at the afferent end of the glomerular capillary to 35 mm at the efferent end, due to the largely protein-free composition of the ultrafiltrate.[14,19] Since the protein concentration of ultrafiltrate is very close to zero, π_T is negligible and $\Delta\pi = \pi_{GC}$. Therefore, the local net ultrafiltration pressure (P_{UF}), which is given by the expression

$$P_{UF} = P_{GC} - P_T - \pi_{GC}$$

declines from a maximum value of some 15 mm of mercury at the afferent end of the capillary to zero by the efferent end. As can be seen in Chart 1, this decline in P_{UF} is the consequence primarily of the rise in $\Delta\pi$. In other words, it has been shown that by the efferent end of the capillary $\Delta\pi$ rises to a value which, on average, exactly equals ΔP.[14,19-21] This equality of ΔP and $\Delta\pi$ is referred to as filtration pressure equilibrium. To summarize the results of these new direct pressure measurements: (1) ΔP is much lower than previously believed; (2) the finding that $\Delta P = \Delta\pi$ by the efferent end of capillary suggests that some portion of the total capillary does not normally contribute to net ultrafiltrate formation; and (3) since the area between the ΔP and $\Delta\pi$ curves (the shaded area in Chart 1) is equal to the mean ultrafiltration pressure, these recent measurements indicate that the mean ultrafiltration pressure is much lower than was previously thought, averaging only 5 to 6 mm of mercury in the normally hydrated rat, rather than earlier estimates of 25 to 35 mm. Of interest in this regard, Maddox and co-workers recently obtained evidence[22] to indicate that the situation in primates is much like that described for rats. Based on similarly direct measurements in squirrel monkeys with accessible surface glomeruli, the evidence indicates that the glomerular transcapillary pressures are virtually the same as in mutant Wistar rats, and that filtration pressure equilibrium is also achieved.

In studies in rats designed to determine how glomerular transcapillary pressures vary so as to bring about changes in SNGFR, evidence has been obtained to indicate that such changes in SNGFR result largely from variations in the rate of rise of $\Delta\pi$, rather than from large or important changes in ΔP.[19-21] Indeed, ΔP appears to be quite effectively autoregulated.[20] Changes in the contour of the $\Delta\pi$ curve arise as a result of changes in the rate of glomerular plasma flow, with increases in the latter tending to displace the point at which filtration pressure equilibrium is reached further to the efferent end of the capillary. The area between the ΔP and $\Delta\pi$ curves is thus increased and the resulting increase in mean ultrafiltration pressure (the area between the ΔP and $\Delta\pi$ curves) brings about an increase in SNGFR. A reduction in glomerular plasma flow has the opposite effect, namely, to displace the equilibrium point further to the afferent end of the capillary, thereby reducing the area between the ΔP and $\Delta\pi$ curves. The resulting reduction in mean ultrafiltration pressure is thereby responsible for a reduction in SNGFR. In general, these observations indicate that the process of glomer-

ular ultrafiltration is highly plasma-flow dependent.

The availability of these direct measurements of glomerular transcapillary pressures and flows, heretofore unavailable in the mammalian kidney, has furnished the incentive for developing a complementary theoretical model of the process of glomerular ultrafiltration.[23] In accord with experimental observations,[19-21] the model predicts that changes in SNGFR may be viewed almost entirely as a consequence of changes in glomerular plasma flow rate. Furthermore, the model has been found useful in suggesting experiments[21] that have allowed estimation of the rat glomerular capillary ultrafiltration coefficient (K_f in Equation 1), the product of effective hydraulic permeability and capillary surface area. K_f has been found to be relatively insensitive to changes in glomerular plasma flow rate and the glomerular effective hydraulic conductivity has been determined to be some 50 times larger than that previously reported.[21]

Proximal Tubule

About two-thirds of the glomerular ultrafiltrate is normally reabsorbed by the proximal tubule.[24-26] In this reabsorptive process, the tubule fluid remains isosmotic with respect to plasma, and there is usually no transepithelial concentration gradient established for Na^+.[25-29] Under certain conditions, however, it can be demonstrated that Na^+ reabsorption can occur against an imposed concentration gradient (as during mannitol infusion, which has the effect of lowering the luminal Na^+ concentration to some 30 $mEq \cdot L^{-1}$ below that of plasma), suggesting that Na^+ is actively transported out of this segment.[25,30-33]

That proximal Na^+ reabsorption is an active, energy-dependent process is further supported by recent findings indicating that the proximal tubule of the mammalian nephron can sustain a small but significant transepithelial electrical potential difference (PD) of approximately 2 to 6 mV, lumen negative.[34-39] For Na^+ reabsorption to proceed against this electrical potential gradient, metabolic energy must be expended. Indeed, the generation and maintenance of this transepithelial PD depends on this expenditure of energy, a conclusion based on the findings that the PD reverts to zero when the epithelium is exposed to cold or to ouabain, a known inhibitor of Na^+ transport.[36-38] Additional support for this conclusion derives from the recent findings of Kokko[39] indicating that in the isolated rabbit proximal tubule studied *in vitro,* this PD appears to be critically dependent upon the presence in the tubule lumen of essential metabolic substrates such as glucose and amino acids.

The results of several recent experiments emphasize the importance of aerobic metabolism[40-42] and oxidative phosphorylation[42-44] in the production of metabolic energy, presumably in the form of adenosine triphosphate (ATP) for active Na^+ transport in the proximal tubule. Na^+-K^+-activated ATPase, an enzyme thought to be involved in coupling the transfer of energy from ATP to the Na^+ transport mechanism,[43-46] has been shown to be located along the canalicular infoldings at the bases of epithelial cells (so-called basilar infoldings) as well as along the narrow cleft-like channels between cells (the intercellular channels).[47,48] Indeed, these basilar infoldings appear to contain more than 100 times as much Na^+-K^+-ATPase activity as the luminal brush border.[49]

It would appear, therefore, that the enzymatic machinery necessary for Na^+ transport is located along the intercellular and basilar membranes. Diamond and Bossert,[50] in an extension of the original three-compartment model of Curran and MacIntosh,[51] have proposed that for epithelia which transport Na^+ and H_2O in isotonic proportions (that is, renal proximal tubule, gallbladder, jejunum), the coupling of Na^+ and H_2O movement is mediated by the active transport of Na^+ into the lateral intercellular channels and basal infoldings with H_2O following passively down the imposed osmotic gradient. Cl^- also follows passively, thereby preserving electroneutrality. This process is illustrated schematically in Chart 2. According to this schema, standing osmotic gradients will develop within these paracellular channels, given the assumptions that (1) the apical (luminal) ends of these channels are tightly sealed (so-called tight junctions) and (2) the channels themselves behave as poorly stirred compartments. It may then be reasoned that as Na^+ is transported into these channels, water follows passively but, at least at the apical ends, not at the same rate as that of Na^+ (due to presumed differences in permeability). As a result, a local (apical) hyperosmotic zone or standing osmotic gradient is created. Osmotic H_2O flow (indicated as the stippled area between adjacent cells in Chart 2) is thought to take place along the entire length of the channel. By the time the fluid

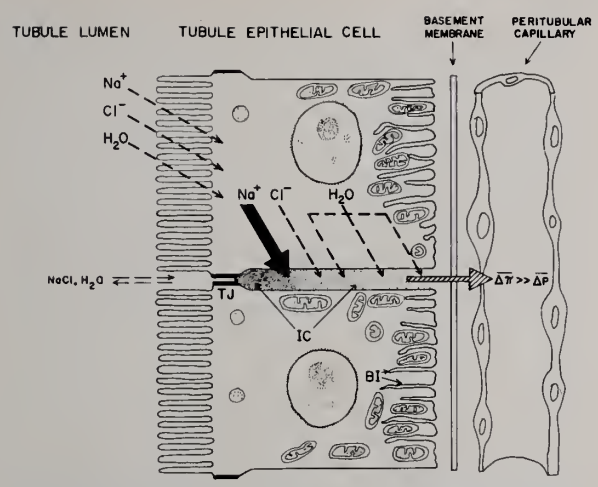


Chart 2.—Idealized proximal tubule epithelial cells under normal hydropenic conditions. (Abbreviations: TJ, tight junction; BI, basilar infoldings; IC, lateral intercellular channel; $\overline{\Delta\pi}$, mean peritubular transcapillary colloid osmotic pressure difference; $\overline{\Delta P}$, mean peritubular transcapillary hydrostatic pressure difference.) Solid black arrow denotes active Na^+ transport. Interrupted arrows denote passive transport. Hatched arrow denotes the path for fluid movement as a function of the peritubular transcapillary Starling forces, $\overline{\Delta\pi}$ and $\overline{\Delta P}$.

reaches the basilar portion of the channel, sufficient osmotic H_2O flow is thought to occur to yield a reabsorbate that is both isotonic and isosmotic with respect to plasma.

The so-called "tight junction" of all epithelia may not be completely impermeable to salt and water. Indeed, the proximal tubule appears to possess a comparatively "leaky" tight junction.[52] It has been shown that the net transport rate of Na^+ out of the proximal tubule is only 20 to 30 percent of the unidirectional efflux of this ion,[29,33] thus indicating extensive back flux due to a high passive permeability of the epithelium to Na^+. Low resistance paracellular ion shunt pathways have recently been shown to exist across mammalian[34,53] and amphibian[54,56] proximal tubules. These have been found to account for as much as 90 to 95 percent of this passive ion movement. The anatomical counterparts of this low resistance pathway are believed to be the "tight junctions" and paracellular channels[55,56] (Chart 2).

In recent years, kidney physiologists have been concerned to a large extent with efforts to isolate and identify the mechanisms controlling isotonic fluid transport across renal proximal tubules. Two lines of evidence have accrued from these efforts which appear to provide at least a partial understanding of the mechanisms involved. The first derives from efforts to demonstrate that the control of proximal reabsorption is governed by factors intrinsic to the epithelium of the proximal convoluted tubule. The studies of Burg and Orloff,[57] Morgan and Berliner,[58] and Earley, Morel, Ullrich, and their respective co-workers[29,59-61] convincingly demonstrate that absolute proximal reabsorption changes sufficiently little in response to selective changes in the filtered load of sodium as to suggest that the proximal tubule is endowed with little intrinsic capacity for self-regulation of salt and water transport.

The second line of evidence derives largely from studies that have focused on the role of the peritubular Starling forces in regulating proximal sodium reabsorption. As early as 1843, Ludwig[4] proposed that passive physical forces might influence net fluid reabsorption by the renal tubule, a suggestion that lay dormant until 1956, when Bresler[62] similarly theorized that the peritubular capillary colloid osmotic pressure (COP) might provide a purely passive driving force for isotonic reabsorption across this segment of the nephron. In support of this view, Vogel, Heym and Andersohn[63] had recently shown that Na^+ reabsorption in the kidneys of amphibians could be enhanced by raising the COP of the peritubular capillary blood. Subsequent studies of Earley, Windhager, Brenner, and their respective co-workers[64-76] and others[38,77-79] have provided additional evidence to support the view that the Starling forces operating across peritubular capillaries exert a strong influence on the reabsorption of salt and water by the proximal tubule.

In order for the oncotic pressure of peritubular capillary plasma to effect the reabsorption of a large fraction of the glomerular filtrate across the proximal tubule by purely passive means, either the transepithelial hydraulic conductivity must be extremely high or the transepithelial osmotic concentration difference must be high, or both. In opposition to these requirements, however, it has been shown that the hydraulic conductivity of the proximal tubule is extremely low,[33,80,81] and a transepithelial osmotic concentration difference as large as that required (20 to 30 $mOsm \cdot L^{-1}$) is not normally found. Therefore, some alternative explanation must be provided to account for this wealth of evidence in favor of a direct relationship between absolute proximal reabsorption and postglomerular COP.

The most attractive explanation to have emerged thus far, that of Lewy and Windhager,[68]

satisfactorily accounts for an action of these physical forces on peritubular capillary uptake and at the same time couples this passive uptake process to the active transport of Na^+ by the proximal tubule epithelium. This coupling is seen to involve the participation of an intermediate compartment (the paracellular channel) situated between tubule lumen and peritubular capillary. Specifically, as shown in Chart 2, Na^+ ions enter the cellular transport pool by passive diffusion down normally existing electrochemical gradients, and are then actively transported into basilar and lateral intercellular channels. Water follows passively, thus elevating pressure in these paracellular channels. This small hydrostatic pressure gradient leads to ultrafiltration of reabsorbate across the tubule basement membrane. The reabsorbate is then moved from the interstitium across the capillary wall, driven by the force defined by the net balance of transcapillary hydrostatic and oncotic pressures. These pressures are denoted in Chart 2 by the symbols $\overline{\Delta P}$ and $\overline{\Delta \pi}$, respectively. Under normal conditions, since $\overline{\Delta \pi}$ greatly exceeds $\overline{\Delta P}$, the net force strongly favors capillary uptake of reabsorbate. In general, any condition that favors a greater increase of $\overline{\Delta \pi}$ over $\overline{\Delta P}$ will result in an increase in net proximal reabsorption. Alternatively, reabsorption will diminish when the balance of transcapillary forces opposes uptake, that is, when $\overline{\Delta \pi}$ no longer greatly exceeds $\overline{\Delta P}$. In the latter case, since capillary uptake of reabsorbate is diminished, egress of fluid at the basilar ends of the paracellular channels is impeded, thereby favoring the passive back flux of ions and water into the tubule lumen. Indeed, under a variety of experimental conditions in which net proximal Na^+ reabsorption is diminished (for example, volume expansion, renal venous occlusion), this passive backflux component for Na^+ has been found to increase dramatically.[38,56,82,83] The effect of this selective decrease in net peritubular capillary uptake on proximal Na^+, Cl^-, and H_2O reabsorption is summarized in Chart 3.

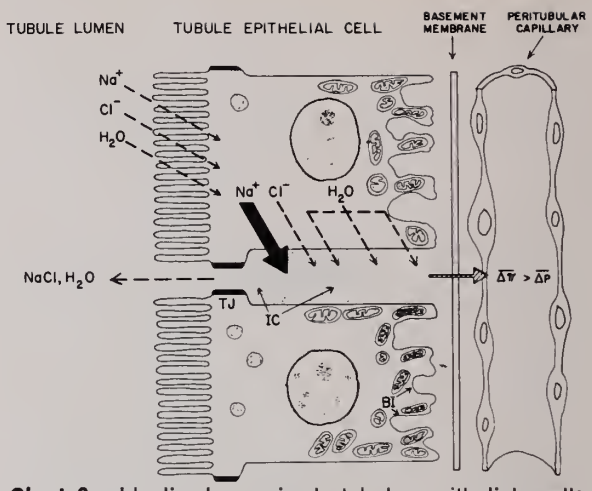


Chart 3.—Idealized proximal tubule epithelial cells under a condition in which peritubular uptake of reabsorbate is diminished (see text). Abbreviations are as given in legend for Chart 2.

Loop of Henle

It is generally accepted that the formation of concentrated urine is the consequence of osmotic equilibration of collecting duct fluid with a hypertonic medullary interstitium. The mechanisms whereby the medullary osmolality is raised are not entirely clear; however, it is thought that the progressive increase in osmolality from the corticomedullary junction to the papillary tip is due to the operation of a countercurrent multiplication system. The operation of the system must have a source of energy. The observation that fluid in the early distal tubule is hypotonic to plasma, while fluid obtained from the bend of the loop is hypertonic, has supported the concept that active outward transport of sodium salts must take place along some portion or all of the ascending limb of Henle's loop.[25,30,84-86]

To study the nature of the operation of the countercurrent multiplier more directly, experiments were devised to examine the composition of fluid obtained from thin limbs of Henle's loops in the papillary tip region *in vivo*.[87] This study showed that fluid from thin ascending limbs is lower in osmolality than fluid obtained from thin descending limbs at comparable levels in the papilla. Furthermore, this hypotonicity of the fluid in ascending limbs was found to be due, not to net addition of H_2O,[88,89] but rather to net removal of solute, primarily NaCl. No conclusion, however, could be reached from these studies regarding the nature of this salt reabsorptive process from the thin ascending limb. Indeed, because of inaccessibility, it is presently impossible to study entire lengths of thin descending and thin ascending limbs of Henle *in vivo*.

Descending Limb of Henle. Recently, however, using the *in vitro* isolated tubule microperfusion technique of Burg et al,[90] Kokko and his associates have been able, in rabbits, to examine directly the NaCl, H_2O, and urea transport characteristics of the thin descending limb of Henle,[91,92] as well as the thin and thick portions

of the ascending limb.[93-95] The thin descending limb was found to be highly permeable to H_2O but to be much less permeable to NaCl and urea. Isotonic fluid enters thin segments of the descending limbs at the corticomedullary junction and equilibrates with the local hypertonic interstitium during its passage toward the papillary tip. Since urea comprises approximately 50 percent of the total osmolality of the papillary interstitium[96-98] and since the osmolality of descending limb fluid equilibrates with that of the adjacent interstitium, it would appear to follow that the NaCl concentration of descending limb fluid should be significantly higher than that of the surrounding interstitium. In rabbits, Kokko estimates that this osmotic equilibration process, which has the effect of raising the NaCl concentration to very high levels by the hairpin turn, occurs almost exclusively (96 percent) by water abstraction and to a far lesser degree (4 percent) by solute entry.[91]

While a number of investigators have demonstrated net water abstraction from the thin descending limb *in vivo*,[86-88,99-102] only Kokko[91] has found this to be the overwhelmingly predominant mechanism for achieving maximal osmolality by the hairpin turn. In these studies by others,[86-88,99-102] solute entry has been found to contribute significantly to the observed elevation in osmolality of tubule fluid by the hairpin turn. Although Kokko has found a high reflection coefficient for urea in *in vitro* perfused thin descending limbs, suggesting little capacity for entry of urea into descending limb fluid, other investigators[89,99,102,103] have reported significant net urea entry *in vivo*. Explanations to account for these differences have yet to be provided.

Remaining to be explored are the possibilities that these differences in results reflect (1) true species variations (studies showing net solute entry were performed in rats, Psammomys, and hamsters,[89,99,102] while Kokko's studies,[91] showing little net solute entry were performed on rabbit tubules), (2) differences due to comparisons of data obtained *in vitro* and *in vivo;* or (3) the fact that Kokko's studies were performed on descending limbs derived from superficial nephrons, whereas in the *in vivo* papillary tip studies, the nephron segments examined were of juxtamedullary origin.[104]

Thin Ascending Limb of Henle. The principal site for active outward transport of NaCl has generally been taken to be the thin ascending limb of Henle's loop. The observation that the fluid within this segment is hypotonic to fluid in adjacent vasa recta and descending limbs at the same level[87,88] is consistent with this view. However, using split droplet techniques,[101] *in vivo* microperfusion techniques,[105] and *in vitro* microperfusion techniques[93,94] for studying ascending limbs, no direct evidence has yet been found to prove that this segment is capable of transporting NaCl actively. A concentration of NaCl lower in the thin ascending limb than in the surrounding interstitium could arise, provided that this segment is H_2O impermeable and that its NaCl permeability is great enough to permit the passive outward diffusion of NaCl at a rate sufficient to render hypotonic the fluid remaining behind. In support of this possibility, Kokko[94] found in *in vitro* microperfusion experiments that the collected perfusate was always lower in NaCl concentration and osmolality than either the initial perfusate or the surrounding bathing medium. Since perfusion fluid and bathing medium had identical osmolalities, whereas the former was relatively rich in NaCl and poor in urea while the reverse was true for the latter, these results are consistent with the view that NaCl can diffuse out of the thin ascending limb more rapidly than urea can diffuse into it. These studies indicate that the thin ascending limb can generate an osmotic gradient, not by active NaCl transport, but rather by purely passive means as a consequence of the differing permeability characteristics of the two thin limbs of Henle to NaCl, urea, and H_2O.

Medullary Thick Ascending Limb of Henle. When the tubule fluid enters the next segment of the nephron, the medullary thick ascending limb of Henle's loop, its relative and absolute amounts of NaCl and urea are lower and higher, respectively, than that of the fluid entering the thin descending limb. The means for lowering NaCl concentration has already been discussed. The elevation in urea concentration appears to take place by two processes: (1) abstraction of water in excess of urea out of the thin descending limb of Henle, and (2) net urea entry (recycled from the collecting duct) into the thin descending and thin ascending limbs of Henle. Using the microperfused isolated rabbit tubule preparation, Kokko[95] has shown that the electrical PD across the medullary thick ascending limb is oriented lumen-positive (approximately +7 mV). This contrasts with the orientation of the PD along other portions of Henle's loop which are typically lumen-negative.[106,107] This finding that the lumen of the thick

ascending limb is electropositive, together with the finding that the NaCl concentration continues to decline as fluid travels along this medullary nephron segment, necessitates the conclusion that Cl^- must be the actively transported moiety.[95] This same conclusion has also been reached by Burg and Green in studies of the isolated cortical thick ascending limb of the rabbit.[108] Since the Na^+ permeability has been found to be greater than that of Cl^-, Cl^- may be regarded as being transported by an electrogenic Cl^- pump while the bulk of the transported Na^+ moves by purely passive means down the existing electrical PD. Besides generating hypotonic tubule fluid, the low water permeability of the thick ascending limb coupled with extensive NaCl efflux gives rise to the well-known high NaCl concentration of the outer medullary interstitium.

Cortical Thick Ascending Limb of Henle. The segment of the thick ascending limb of Henle's loop, which begins at the point where it crosses from the outer medulla into the cortex and extends to the macula densa, is referred to, variously, as the cortical diluting segment, the cortical portion of the thick ascending limb of Henle's loop, or the straight distal tubule. Although the medullary portion of this segment has thicker cells than the cortical portion, the functions of the two parts of the thick ascending limb appear to be similar. As in the case of the medullary thick ascending limb, the cortical thick ascending limb of rabbits has been studied directly by *in vitro* microperfusion techniques.[108] NaCl has been found be be actively reabsorbed across this epithelium of extremely low water permeability (about 1 percent of that of the proximal tubule).

In support of the latter, Burg and Green[108] found essentially no water reabsorption when the fluid perfusing the lumen of this segment was sufficiently dilute to create a large osmotic gradient between tubule lumen and bath, a condition otherwise favoring net water flow. As a result of this absorption of NaCl but not H_2O, luminal fluid becomes hypotonic. This result is in agreement with the observation uniformly obtained in *in vivo* micropuncture studies in a number of species, in that fluid collected from the early distal convoluted tubule has been shown to have low Na^+ concentrations.[24,26,84]

In further accord with the results of studies of the medullary portion of the thick ascending limb,[95] Burg and Green[108] found Cl^- transport in the cortical segment of the thick ascending limb to also be an active, energy-dependent process, since Cl^- concentration decreased in the lumen despite opposing gradients of chemical concentration and electrical potential. The orientation of the electrical PD with lumen-positive across the cortical thick ascending limb results from the active, outward transport of Cl^- and disappears when Cl^- is removed from the lumen and bath, and sulfate or nitrate are substituted.[109] Again as with the medullary portion of the thick ascending limb, Na^+ transport is therefore largely passive.[108,109]

A Passive Equilibration Model of Countercurrent Multiplication. On the basis of the foregoing, Kokko and Rector[110] have proposed a passive equilibration model of countercurrent multiplication to explain the production of concentrated urine. In this model it is envisaged that when the hypotonic fluid leaves the thick ascending limb of Henle's loop and courses through the distal tubule and cortical collecting tubule, it undergoes osmotic equilibration with the surrounding isotonic interstitium by virtue of water abstraction in the presence of antidiuretic hormone (ADH). The permeabilities of the cortical segment of the thick ascending limb of Henle's loop and the distal convoluted tubule to urea are believed to be extremely low. Indeed, Burg et al[111] have shown that even in the presence of ADH the cortical collecting tubule is completely impermeable to urea. Similar results have been obtained by Schafer and Andreoli[112] for the outer medullary collecting duct. Thus, the urea concentration in the fluid entering the cortical collecting duct is extremely high and rises further as the collecting duct passes through the outer medulla. This progressive rise in urea concentration is the consequence of water removal, which, in turn, is secondary to the high NaCl concentration in the surrounding outer medullary interstitium. This high urea concentration in the collecting duct fluid persists until the fluid reaches the inner medulla where, because of a pronounced local *increase* in collecting duct permeability to urea, urea now diffuses down its concentration gradient into the papillary interstitium.[113]

To a variable extent, as already discussed, urea is recycled into thin descending and thin ascending limbs. In terms of the passive equilibration model, however, the main function of this high interstitial urea concentration is to exert an osmotic effect on thin descending limbs, favoring abstraction of H_2O and raising the concentration

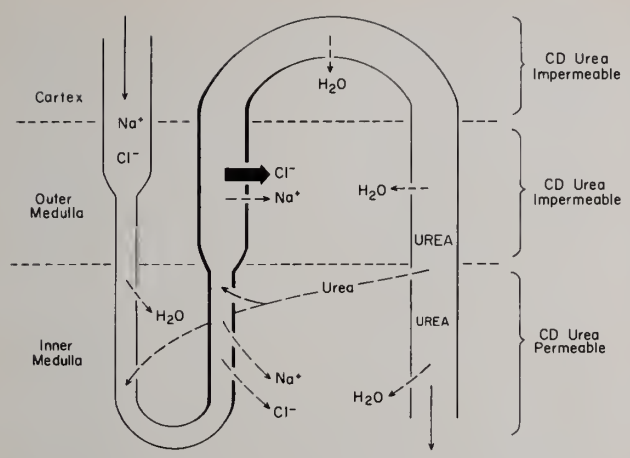


Chart 4.—A schema of countercurrent multiplication by means of passive equilibration of solute in the renal medulla. Solid black arrow denotes active Cl^- transport. Interrupted arrows denote passive transport. The portion of the collecting duct (CD) in the cortex and outer medulla is urea impermeable, whereas the inner medullary CD is highly urea permeable. The solid dark lines along the ascending limb of Henle denote water impermeability. Nephron segments downstream to the ascending limb are shown to be water permeable due to the presence of ADH (modified from Kokko and Rector[110]).

of intraluminal NaCl. The thin ascending limb, in turn, is presented with a hypertonic fluid rich in NaCl. Because the thin ascending limb is impermeable to H_2O, slightly permeable to urea, and highly permeable to NaCl, the latter can diffuse down concentration gradients at rates faster than the inward diffusion of urea, leading to progressive hypotonicity of the fluid as it flows toward the renal cortex. The combination of these processes could then account for the observed progressive rise in the interstitial osmolality from the corticomedullary junction to the papillary tip. An idealized version of how the limbs of Henle and collecting duct serve to favor passive equilibration of solute in the region of the papilla, as proposed by Kokko and Rector,[110] is summarized in Chart 4.

In the intact animal, the fluid that leaves the cortical thick ascending limb of Henle is low in Na^+ and Cl^- concentration, and the concentrations of these ions are largely independent of the animal's state of hydration or diet. Were this fluid to be excreted without further modification, the urine would always be dilute. Usually, however, urine does not have these characteristics but instead its composition is altered further by the action of other transport processes located in more distal nephron segments.

Distal Nephron

The remaining part of the nephron consists of several anatomically and physiologically discrete tubule segments which, together, account for a substantial fraction of the overall reabsorption of NaCl. Control of urinary dilution and concentration (that is, H_2O reabsorption) and the final modulation of net potassium excretion occur in these nephron segments as well. In addition, hormones such as ADH and aldosterone and a number of the clinically useful diuretic drugs are believed to exert major effects here.[114]

The Distal Convoluted Tubule. This segment is conventionally described as that portion of the nephron extending from the macula densa to its junction with one or more other distal convoluted tubules to form the cortical collecting tubule. This segment has been extensively studied by conventional micropuncture techniques in rats, dogs and monkeys.[24,26,84,85] In rats, H_2O reabsorption by this segment is variable, depending on the state of hydration and, more specifically, on the presence or absence of ADH.[115] In the absence of ADH, this and more distal nephron segments are essentially impermeable to H_2O, so that the hypotonic fluid entering this segment is excreted as dilute urine. Indeed, continued NaCl reabsorption along the distal convoluted tubule results in further dilution of the urine in the absence of ADH. In the presence of ADH in rats, the permeability of the late portion of this segment to H_2O increases greatly. As a result, the osmolality of late distal tubule fluid rises to a value close to that of plasma. There is disagreement among investigators as to whether the fluid equilibrates completely with the surrounding isosmotic interstitium, but all agree that an increase in osmolality toward that of plasma is achieved.[116] In dogs[24,85] and monkeys,[26] the situation in the absence of ADH is similar to that described for rats. In the presence of ADH, however, the evidence thus far seems clear that full osmotic equilibration (fluid-to-plasma osmolality ratio of unity) with the surrounding isosmotic interstitium does not take place along the late distal tubule. Instead, fluid-to-plasma osmolality ratios achieve values of approximately 0.8. In dogs and monkeys, and in those groups of rats which fail to reach osmotic equilibration by the late distal convoluted tubule, isosmolality is achieved in the cortical collecting tubule.

The electrolyte transport system in the distal convoluted tubule has been studied extensively.[84,117,118] It is generally observed that NaCl

continues to be reabsorbed from the tubule lumen.[24,26,84] In rats, net Na^+ reabsorption proceeds uphill against a moderately steep chemical concentration gradient[118] and against an electrical potential gradient which increases from −12 mV (lumen-negative) in the early distal tubule to about −45 mV (lumen-negative) by the late tubule.[119] In the absence of aldosterone, the capacity of the epithelium of the distal tubule to lower the Na^+ concentration in tubule fluid has been shown to be reduced.[120] From calculations using the Nernst equation, which describes the distribution of charged ions across a membrane under conditions of diffusion equilibrium, the transport of Cl^- to a large extent can be ascribed to purely passive forces, namely, diffusion down an electrical PD from tubule lumen to peritubular capillary blood. That Cl^- might also be transported by an active extrusion mechanism in this segment was first suggested by Rector and Clapp.[121] Recent evidence by Malnic and Giebisch[122] offers further support for this conclusion. As with rats, dogs have recently been shown to be capable of transporting NaCl against steep electrochemical gradients.[34]

Cortical Collecting Tubule. This segment extends unbranched from the junctions of distal convoluted tubules, through the cortex to the junction with other cortical collecting tubules in the outer medulla. This segment has been the subject of extensive recent investigations using the technique of microperfusion of isolated rabbit tubule fragments.[123-126] These studies demonstrated that this epithelium possesses an extremely low permeability to H_2O in the absence of ADH and that this permeability increases greatly in the presence of this hormone. The sensitivity of this segment to ADH appears to be more pronounced than is that of the distal convoluted tubule. Urea permeability has been found to be low and, as discussed above, to be remarkably insensitive to ADH. This unresponsiveness of urea permeability to ADH is considered essential to the efficient recycling of urea in the operation of the passive equilibration model of urine concentration discussed above.

Studies on the nature of electrolyte transport using microperfusion techniques indicate that this segment is capable of further net reabsorption of NaCl. The rate of Na^+ transport here is considerably lower than that of the proximal convoluted tubule and more like that of the distal convoluted tubule. In microperfusion studies of this segment in the rabbit, the transepithelial PD is about 35 mV (lumen-negative).[109] By comparing the theoretical PD based on the differences in the concentrations of electrolytes in the luminal fluid and surrounding bathing medium with the PD actually measured,[125] and by studying the flux ratios for Na^+ and Cl^-,[109] it appears that Na^+ reabsorption is active and that Cl^- reabsorption can be accounted for entirely by passive means.

Papillary Collecting Duct. The terminal segment of the distal nephron is the highly branched papillary collecting duct. This segment has been studied in rats[127,128] and hamsters,[129] both by micropuncture of the surface of the papilla exposed by dissection of the renal pelvis, and also by retrograde catheterization from the tip of the papilla. These more recent direct studies have generally supported earlier conclusions based on comparisons of data obtained from late distal sites with final urine.[84] Continued electrolyte transport in this segment results in the typically large ion concentration differences that normally exist between urine and plasma. Na^+ transport appears to be active, since reabsorption proceeds against sizable electrochemical gradients.[129,130] The rate of Na^+ transport in this segment depends on the diet and on the load of sodium delivered from earlier segments[128] and is affected by the presence or absence of aldosterone.[131] It would also appear that this segment has the ability to effect active Cl^- reabsorption.[128] Water permeability increases markedly in the presence of ADH,[132] an effect similar to that seen in the distal convoluted tubule and cortical collecting tubule. Importantly, the papillary collecting duct differs from these latter structures in that its permeability to urea increases dramatically in the presence of ADH. For the reasons noted above, the high H_2O and urea permeability of the papillary collecting duct in the presence of ADH appears to be of fundamental importance to the formation of hypertonic urine.

Thus, there are at least three distinct segments of the distal nephron—the distal convoluted tubule, the cortical collecting tubule, and the papillary collecting duct. The electrical potential differences of these segments vary somewhat, but so far have always been found to be lumen-negative. In each segment there is net NaCl reabsorption. Active Na^+ transport predominates in all segments. Evidence has been cited to indicate that Cl^- can be actively transported from the distal convoluted tubule and papillary collecting duct, whereas in the cortical collecting duct, Cl^- has

been found thus far only to be transported passively. Water permeability is variable in distal nephron segments, depending on the presence or absence of ADH. Urea permeability is low and unaffected by ADH in all segments except the papillary collecting duct, where the increased permeability to urea in the presence of ADH appears to be important in the recycling of urea and the production of hypertonic urine.

Summary

The aim of this review has been to provide a current survey of our present knowledge of the mechanisms governing sodium chloride and water transport across the various anatomical segments of the mammalian nephron. We have dealt more completely with those aspects of renal salt and water transport that have recently yielded new insights (for example, glomerular ultrafiltration, the passive function of the thin limbs of Henle) than with areas of knowledge that have tended to change little in recent years. Limitations of space have precluded extensive discussion of the intrarenal and extrarenal factors governing the control of sodium excretion. Nor have we been able to review the extensive progress that has been made in areas of renin-angiotensin-aldosterone interaction and regulation of regional distribution of renal blood flow. For current thinking in these fields, the reader is referred elsewhere for excellent summaries.[133-142]

REFERENCES

1. Richards AN, Schmidt CF: A description of the glomerular circulation of the frog's kidney and observations concerning the action of adrenalin and various other substances upon it. Am J Physiol 71:178-208, 1924

2. Wearn JT, Richards AN: Observations on the composition of glomerular urine, with particular reference to the problem of reabsorption in the renal tubules. Am J Physiol 71:209-227, 1924

3. Walker AM: Comparison of total molecular concentration of glomerular urine and blood plasma from the frog and from necturus. J Biol Chem 87:499-522, 1930

4. Ludwig C: Beiträge zur Lehre vom Mechanismus der Harnsecretion. Marburg, Elwert, 1843

5. Walker AM, Bott PA, Oliver J, MacDowell MC: The collection and analysis of fluid from single nephrons of the mammalian kidney. Am J Physiol 134:580-595, 1941

6. Starling EH: On the absorption of fluids from the connective tissue spaces. J Physiol (London) 19:312-326, 1896

7. Starling EH: The glomerular functions of the kidney. J Physiol (London) 24:317-330, 1899

8. Landis EM: Micro-injection studies of capillary permeability —II. The relationship between capillary pressure and the rate at which fluid passes through the walls of single capillaries. Am J Physiol 82:217-238, 1927

9. Zweifach, BW, Intaglietta M: Mechanics of fluid movement across single capillaries in the rabbit. Microvasc Res 1:83-101, 1968

10. Pappenheimer JR, Soto-Rivera A: Effective osmotic pressure of the plasma proteins and other quantities associated with the capillary circulation in the hind limb of cats and dogs. Am J Physiol 152:471-491, 1948

11. Smaje L, Zweifach BW, Intaglietta M: Micropressures and capillary filtration coefficients in single vessels of the cremaster muscle of the rat. Microvasc Res 2:96-110, 1970

12. Hayman JM Jr: Estimations of afferent arteriole and glomerular capillary pressures in frog kidney. Am J Physiol 79: 389-409, 1927

13. White HL: Observations on the nature of glomerular activity. Am J Physiol 90:689-704, 1929

14. Brenner BM, Troy JL, Daugharty TM: The dynamics of glomerular ultrafiltration in the rat. J Clin Invest 50:1776-1780, 1971

15. Gertz KH, Mangos JA, Braun G, et al: Pressure in the glomerular capillaries of the rat kidney in relation to arterial blood pressure. Pflügers Arch 288:369-374, 1966

16. Gertz KH, Brandis M, Braun-Schubert G, et al: The effect of saline infusion and hemorrhage on glomerular filtration pressure and single nephron filtration rate. Pflügers Arch 310:193-205, 1969

17. Gottschalk CW, Mylle M: Micropuncture study of pressures in proximal tubules and peritubular capillaries of the rat kidney and their relation to ureteral and renal venous pressures. Am J Physiol 185:430-439, 1956

18. Blantz RC, Israelit AH, Rector FC Jr, et al: Relation of distal tubular NaCl delivery and glomerular hydrostatic pressure. Kidney Int'l 2:22-32, 1972

19. Brenner BM, Troy JL, Daugharty TM, et al: Dynamics of glomerular ultrafiltration in the rat—II. Plasma-flow dependence of GFR. Am J Physiol 223:1184-1190, 1972

20. Robertson CR, Deen WM, Troy JL, et al: Dynamics of glomerular ultrafiltration in the rat—III. Hemodynamics and autoregulation. Am J Physiol 223:1191-1200, 1972

21. Deen WM, Troy JL, Robertson CR, et al: Dynamics of glomerular ultrafiltration in the rat—IV. Determination of the ultrafiltration coefficient. J Clin Invest 52:1500-1508, 1973

22. Maddox DA, Deen WM, Brenner BM: Dynamics of glomerular ultrafiltration—VI. Studies in the primate. Kidney Int'l. In press

23. Deen WM, Robertson CR, Brenner BM: A model of glomerular ultrafiltration in the rat. Am J Physiol 223:1178-1183, 1972

24. Bennett CM, Clapp JR, Berliner RW: Micropuncture study of the proximal and distal tubule in the dog. Am J Physiol 213: 1254-1262, 1967

25. Ullrich KJ, Schmidt-Nielsen B, O'Dell R, et al: Micropuncture study of composition of proximal and distal fluid in rat kidney. Am J Physiol 204:527-531, 1963

26. Bennett CM, Brenner BM, Berliner RW: Micropuncture study of nephron function in the Rhesus monkey. J Clin Invest 47:203-216, 1968

27. Jamison RL: Micropuncture study of superficial and juxtamedullary nephrons in the rat. Am J Physiol 218:46-55, 1970

28. Lassiter WE, Gottschalk CW, Mylle M: Micropuncture study of net transtubular movement of water and urea in nondiuretic mammalian kidney. Am J Physiol 200:1139-1146, 1961

29. Morel F, Murayama Y: Simultaneous measurement of unidirectional and net sodium fluxes in microperfused rat proximal tubules. Pflügers Arch 320:1-23, 1970

30. Windhager EE, Giebisch G: Micropuncture study of renal tubular transfer of sodium chloride in the rat. Am J Physiol 200: 581-590, 1961

31. Giebisch G, Klose RM, Malnic G, et al: Sodium movement across single perfused tubules of rat kidneys. J Gen Physiol 47:1175-1194, 1964

32. Ullrich KJ: Renal transport of sodium, *In* Proc 3rd Int'l Congr Nephrol Washington, 1966, Vol. 1. Karger, Basel/New York, 1967, pp 48-61

33. Kokko JP, Burg MB, Orloff J: Characteristics of NaCl and water transport in the renal proximal tubule. J Clin Invest 50: 69-76, 1971

34. Boulpaep EL, Seely JF: Electrophysiology of proximal and distal tubules in the autoperfused dog kidney. Am J Physiol 221: 1084-1096, 1971

35. Mello GB de, Malnic G: Algunas características electrofysiológicas de túbulos proximais de rins de rato. Proc Congr Soc Brasileira Paro Progr, Ciencia, 22nd, p 326, 1970

36. Burg MB, Orloff J: Electrical potential difference across proximal convoluted tubules. Am J Physiol 219:1714-1716, 1970

37. Kokko JP, Rector FC: Flow dependence of transtubular potential difference in isolated perfused segments of rabbit proximal convoluted tubules. J Clin Invest 50:2745-2750, 1971

38. Imai M, Kokko JP: Effect of peritubular protein concentration on reabsorption of sodium and water in isolated perfused proximal tubule. J Clin Invest 51:314-325, 1972

39. Kokko JP: Proximal tubule potential difference. Dependence on glucose, HCO_3, and amino acids. J Clin Invest 52:1362-1367, 1973

40. Weinstein SW, Klose RM: Micropuncture studies on energy metabolism and sodium transport in the mammalian nephron. Am J Physiol 217:498-504, 1969

41. Martinez-Maldonado M, Eknoyan G, Suki WN: Effects of cyanide on renal concentration and dilution. Am J Physiol 217: 1363-1368, 1969

42. Györy AZ, Kinne R: Energy source for transepithelial sodium transport in rat renal proximal tubule. Pflügers Arch 327: 234-260, 1971

43. Macknight ADC: The effects of ethacrynic acid on the electrolyte and water contents of rat renal cortical tissues. Biochim et Biophys Acta 173:223-233, 1969

44. Whittemburry G, Proverbio F: Two modes of Na extrusion in cells from Guinea-pig kidney cortex slices. Pflügers Arch 316: 1-25, 1970

45. Skou JC: Enzymatic basis for active transport of Na^+ and K^+ across cell membrane. Physiol Rev 45:596-617, 1965

46. Proverbio F, Robinson JW, Whittembury G: Sensitivities of Na^+-K^+-ATPase and Na^+ extrusion mechanisms to ouabain and ethacrynic acid in the cortex of Guinea-pig kidney. Biochim et Biophys Acta 211:327-336, 1970

47. Goldfischer S, Essner E, Novikoff AB: The localization of phosphatase activity at the level of ultrastructure. J Histochem Cytochem 12:72-95, 1964

48. Kinne R. Schmitz JE, Kinne-Saffran E: The localization of the Na^+-K^+-ATPase in the cells of the rat kidney cortex. Pflügers Arch 329:191-206, 1971

49. Schmidt U, Dubach UC: Na-K Stimulated adenosinetriphosphatase: Intracellular localization within the proximal tubule of the rat kidney. Pflügers Arch 330:265-270, 1971

50. Diamond JM, Bossert WH: Standing-gradient osmotic flow. J Gen Physiol 50:2061-2082, 1967

51. Curran PF, MacIntosh JR: A model system for biological water transport. Nature (London) 193:347-348, 1962

52. Frömter E, Diamond J: The route of passive ion permeation in epithelia. Nature (New Biology) 235:9-13, 1972

53. Hegel U, Frömter E, Wick T: Der electrische wandwiderstand des proximalen konvolutes der rattenniere. Pflügers Arch 294:274-290, 1967

54. Windhager EE, Boulpaep EL, Giebisch G: Electrophysiological studies on single nephrons. Proc 3rd Int'l Congr Nephrol Washington, 1966, Vol 1. Karger, Basel/New York, 1967, pp 35-47

55. Whittembury G, Rawlins FA: Evidence of a paracellular pathway for ion flow in the kidney proximal tubule: Electromicroscopic demonstration of lanthanum precipitate in the tight junction. Pflügers Arch 330:302-309, 1971

56. Boulpaep EL: Permeability changes of the proximal tubule of Necturus during saline loading. Am J Physiol 222:517-531, 1972

57. Burg MB, Orloff J: Control of fluid absorption in the renal proximal tubule. J Clin Invest 47:2016-2024, 1968

58. Morgan T. Berliner RW: *In vivo* perfusion of proximal tubules of the rat—Glomerulotubular balance. Am J Physiol 217: 992-997, 1968

59. Buentig WE: Earley LE: Demonstration of independent roles of proximal tubular reabsorption and intratubular load in the phenomenon of glomerulotubular balance during aortic constriction in the rat. J Clin Invest 50:77-89, 1971

60. Radtke HW, Rumrich A, Klan S, et al: Influence of luminal diameter and flow velocity on the isotonic fluid absorption and ^{36}Cl permeability of the proximal convolution of the rat kidney. Pflügers Arch 324:288-296, 1971

61. Bartoli E, Earley LE: Importance of ultrafilterable plasma factors in maintaining tubular reabsorption. Kidney Int'l 3:142-150, 1973

62. Bresler EH: The problem of the volume component of body fluid homeostasis. Am J Med Sci 232:93-104, 1956

63. Vogel A, Heym E, Andersohn K: Versuche zur Bedeutung kolloidosmotischer Durckdifferenzen für einen passiven Trantportmechanismus in den nierenkanälchen. Z Ges Exptl Med 126:485-495, 1955

64. Earley LE, Friedler RM: The effects of combined renal vasodilatation and pressor agents on renal hemodynamics and the tubular reabsorption of sodium. J Clin Invest 45:542-551, 1966

65. Earley LE, Martino JA, Friedler RM: Factors affecting sodium reabsorption by proximal tubule as determined during blockade of distal sodium reabsorption. J Clin Invest 45:1668-1684, 1966

66. Martino JA, Earley LE: Demonstration of a role of physical factors as determinants of the natriuretic response to volume expansion. J Clin Invest 46:1963-1978, 1967

67. Daugharty TM, Belleau LJ, Martino JA, et al: Interrelationship of physical factors affecting sodium reabsorption in the dog. Am J Physiol 215:1442-1447, 1968

68. Lewy JE, Windhager EE: Peritubular control of proximal tubular fluid reabsorption in the rat kidney. Am J Physiol 214: 943-954, 1968

69. Spitzer A, Windhager EE: Effect of peritubular oncotic pressure changes on proximal fluid reabsorption. Am J Physiol 218:1188-1193, 1970

70. Brenner BM, Falchuk KH, Keimowitz RI, et al: The relationship between peritubular capillary protein concentration and fluid reabsorption by the renal proximal tubule. J Clin Invest 48: 1519-1531, 1969

71. Falchuk KH, Brenner BM, Tadokoro M, et al: Oncotic and hydrostatic pressures in peritubular capillaries and fluid reabsorption by proximal tubule. Am J Physiol 220:1427-1433, 1971

72. Brenner BM, Galla JH: Influence of postglomerular hematocrit and protein concentration on rat nephron fluid transfer. Am J Physiol 220:148-161, 1971

73. Brenner BM, Troy JL: Postglomerular vascular protein concentration: Evidence for a causal role in governing fluid reabsorption and glomerulotubular balance by the renal proximal tubule. J Clin Invest 50:336-349, 1971

74. Brenner BM, Troy JL, Daugharty TM: On the mechanism of inhibition in fluid reabsorption by the renal proximal tubule of the volume-expanded rat. J Clin Invest 50:1596-1602, 1971

75. Daugharty TM, Ueki IF, Nicholas DP, et al: Comparative renal effects of isoncotic and colloid-free volume expansion in the rat. Am J Physiol 222:225-235, 1972

76. Brenner BM, Troy JL, Daugharty TM, et al: Quantitative importance of changes in postglomerular colloid osmotic pressure in mediating glomerulotubular balance in the rat. J Clin Invest 52:190-197, 1973

77. Nizet A: Influence of serum albumin and dextran on sodium and water excretion by the isolated dog kidney. Pflügers Arch 301: 7-15, 1968

78. Vereerstraeten P, de Myttenaere M: Effect of raising the transtubular oncotic pressure gradient on sodium excretion in the dog. Pflügers Arch 302:1-12, 1968

79. Vereerstraeten P, Toussaint C: Role of the peritubular oncotic pressure on sodium excretion by the avian kidney. Pflügers Arch 302:13-23, 1968

80. Ullrich KJ, Rumrich G, Fuchs G: Wasserpermeabilität und transtubulärer Wasserfluss corticoler Nephronabschnitte bei verschiedenen Diuresezuständen. Pflügers Arch 280:99-119, 1964

81. Welling LW, Grantham JJ: Physical properties of isolated perfused renal tubules and tubular basement membranes. J Clin Invest 51:1063-1075, 1972

82. Bank N, Yarger WE, Aynedjian HS: A microperfusion study of sucrose movement across the rat proximal tubule during renal vein constriction. J Clin Invest 50:294-302, 1971

83. DiBona DR, Civan MM: Pathways for movement of ions and water across toad urinary bladder—I. Anatomic site of transepithelial shunt pathways. J Membrane Biol 12:101-128, 1973

84. Malnic G, Klose RM, Giebisch G: Micropuncture study of distal tubular potassium and sodium transport in rat nephron. Am J Physiol 211:529-547, 1966

85. Clapp JR, Robinson RR: Osmolality of distal tubular fluid in the dog. J Clin Invest 45:1847-1858, 1966

86. Gottschalk CW, Lassiter WE, Mylle M, et al: Micropuncture study of composition of loop of Henle fluid in desert rodents. Am J Physiol 204:532-535, 1963

87. Jamison RL, Bennett CM, Berliner RW: Countercurrent multiplication by thin loops of Henle. Am J Physiol 212:357-366, 1967

88. Jamison RL: Micropuncture study of segments of thin loop of Henle in the rat. Am J Physiol 215:236-242, 1968

89. Marsh DJ: Solute and water flows in thin limbs of Henle's loop in the hamster kidney. Am J Physiol 218:824-831, 1970

90. Burg M, Grantham J, Abramow M, et al: Preparation and study of fragments of single rabbit nephrons. Am J Physiol 210: 1293-1298, 1966

91. Kokko JP: Urea transport in the proximal tubule and the descending limb of Henle. J Clin Invest 51:1999-2008, 1972

92. Kokko JP: Sodium chloride and water transport in the descending limb of Henle. J Clin Invest 49:1838-1846, 1970

93. Imai M, Kokko JP: Sodium chloride, urea and water transport in the thin ascending limb of Henle—Generation of osmotic gradients by passive diffusion of solutes. J Clin Invest (In press)

94. Kokko JP: Membrane characteristics governing salt and water transport in the loop of Henle. Fed Proc (In press)

95. Kokko JP: Sodium chloride and water transport in the medullary thick ascending limb of Henle. J Clin Invest 52:612-623, 1973

96. Levitin H, Goodman A, Pigeon G, et al: Composition of the renal medulla during water diuresis. J Clin Invest 41:1145-1151, 1962

97. Ullrich KJ, Jarausch KH: Untersuchungen zum Problem der Karnhonzentrierung undurdünnung. Uber die Verteilung der Elektrolyten (Na, K, Ca, Mg, Cl, anorg. Phosphat), Harnstoff, Aminosäuren und exogenem Kreatinin in Rinde und Mark der Hendeniere bei verschiedenen Diuresezustanden. Pflügers Arch 262:537-550, 1956

98. Valtin H: Sequestration of urea and nonurea solutes in renal tissues of rats with hereditary hypothalamic diabetes insipidus—Effect of vasopressin and dehydration on the countercurrent mechanism. J Clin Invest 45:337-345, 1966

99. Jamison RL, Buerkero J, Lacy F: A micropuncture study of Henle's thin loop in Brattleboro rats. Am J Physiol 224:180-185, 1973

100. Lassiter WE, Mylle M, Gottschalk CW: Micropuncture study of urea transport in rat renal medulla. Am J Physiol 210: 965-970, 1966

101. Marsh DJ, Solomon S: Analyzing electrolyte movement in thin Henle's loop of hamster papilla. Am J Physiol 208:1119-1128, 1965

102. de Rouffignac C, Morel F: Micropuncture study of water, electrolytes, and urea movement along the loops of Henle in Psammomys. J Clin Invest 48:474-486, 1969

103. Pennell JP, Lacy FB, Frey NR, et al: Comparison of urea concentrations in fluid from Henle's loop and collecting duct. Clin Res 21:702, 1973 (Abs)

104. Jamison RL: Intrarenal heterogeneity—The case for two functionally dissimilar populations of nephrons in the mammalian kidney. Am J Med 54:281-289, 1973

105. Morgan T, Berliner RW: Permeability of the loop of Henle, vasa recta and collecting duct to water, urea and sodium. Am J Physiol 215:108-115, 1968

106. Windhager EE: Electrophysiological study of renal papilla of golden hamsters. Am J Physiol 206:694-700, 1964

107. Windhager EE, Giebisch G: Electrophysiology of the nephron. Physiol Rev 45:214-244, 1965

108. Burg MB, Green N: Function of the thick ascending limb of Henle's loop. Am J Physiol 224:659-668, 1973

109. Burg MB, Stoner L: Sodium transport in the distal nephron. Fed Proc (In press)

110. Kokko JP, Rector FC: Countercurrent multiplication system without active transport in inner medulla. Kidney Int'l 2: 214-223, 1972

111. Burg M. Helman S, Grantham J, Orloff J: Urea and the Kidney, Amsterdam, Excerpta Medica, 1970, pp 193-199

112. Schafer JA, Andreoli TE: The effect of antidiuretic hormone on solute flows in mammalian collecting tubules. J Clin Invest 51:1279-1286, 1972

113. Morgan T, Sakai F, Berliner RW: *In vitro* permeability of medullary collecting ducts to water and urea. Am J Physiol 214: 574-581, 1968

114. Frazier HS, Yager H: The clinical use of diuretics. N Engl J Med 288:246-252, 1973

115: Gottschalk CW: Micropuncture studies of tubular function in the mammalian kidney. The Physiologist 4:35-55, 1961

116. Colindres RE, Lethene C: Technical problems associated with collection of distal tubular fluid in the rat. Yale J Biol and Med 45:233-239, 1972

117. Malnic G, Klose RM, Giebisch G: Micropuncture study of renal potassium excretion in the rat. Am J Physiol 206:674-686, 1964

118. Malnic G, Klose RM, Giebisch G: Microperfusion study of distal tubular potassium and sodium transfer in rat kidney. Am J Physiol 211:548-559, 1966

119. Wright F: Increasing magnitude of electrical potential along the renal distal tubule. Am J Physiol 220:624-638, 1971

120. Hierholzer K, Wiederholt M. Holzgreve H, et al: Micropuncture study of renal transtubular concentration gradients of sodium and potassium in adrenalectomized rats. Pflügers Arch 285:193-210, 1965

121. Rector FC, Clapp JR: Evidence for active chloride reabsorption in the distal renal tubule of the rat. J Clin Invest 41:101-107, 1962

122. Malnic G, Giebisch G: Some electrical properties of distal tubular epithelium in the rat. Am J Physiol 223:797-808, 1972

123. Grantham JJ, Burg MB: Effect of vasopressin and cyclic AMP on permeability of isolated collecting tubules. Am J Physiol 211:255-259, 1966

124. Helman SI, Grantham JJ, Burg MB: Effect of vasopressin on electrical resistance of renal cortical collecting tubules. Am J Physiol 220:1825-1832, 1971

125. Grantham JJ, Burg MB, Orloff J: The nature of transtubular Na and K transport in isolated rabbit renal collecting tubules. J Clin Invest 49:1815-1826, 1970

126. Frindt G, Burg MB: Effect of vasopressin on sodium transport in renal cortical collecting tubules. Kidney Int'l 1:224-231, 1972

127. Jamison RL, Buerkert J, Lacy F: A micropuncture study of collecting tubule function in rats with hereditary diabetes insipidus. J Clin Invest 50:2444-2452, 1971

128. Diezi J, Michaud P, Aceves J, et al: Micropuncture study of electrolyte transport across papillary collecting duct of the rat. Am J Physiol 224:623-634, 1973

129. Laurence R, Marsh DJ: Effect of diuretic states on hamster collecting duct electrical potential differences. Am J Physiol 220: 1610-1616, 1971

130. Sakai J, Jamison RL, Berliner RW: A method for exposing the rat renal medulla *in vivo:* Micropuncture of the collecting duct. Am J Physiol 209:663-668, 1965

131. Uhlich E, Baldamus CA, Ullrich KJ: Einfluss von Aldosteron auf den Natriumtransport in den Sammelrohren der Säugetierniere. Pflügers Arch 308:111-126, 1969

132. Morgan T: Permeability of the nephron to urea, *In* Urea and the Kidney, Amsterdam, Excerpta Medica, 1970, pp 180-192

133. Walzer M: Sodium excretion, *In* The Kidney, Vol III. New York, Academic Press, 1971, pp 128-208

134. DeWardener HE: Control of sodium reabsorption. Br Med J 3:611-616 and 3:676-683, 1969

135. Earley LE, Daugharty TM: Sodium metabolism. N Engl J Med 281:72-86, 1969

136. Schrier RW, DeWardener HE: Tubular reabsorption of sodium ion—Influence of factors other than aldosterone and glomerular filtration rate. N Engl J Med 285:1231-1243 and 285: 1292-1303, 1971

137. Bricker NS, Klahr S: The physiological basis of sodium excretion and diuresis, *In* Advances in Internal Med, Vol 16. Chicago, Year Book Medical Publishers, 1970, pp 17-41

138. Barger AC, Herd JA: The renal circulation. N Engl J Med 284:482-490, 1971

139. Stein JH, Boonjarern S, Wilson CB, Ferris TF: Alterations in intrarenal blood flow distribution—Methods of measurement and relationship to sodium balance. Circ Res 32:Supplement No 1, I-61—I-72, 1973

140. Vander AJ: Control of renin release. Physiol Rev 47:359-382, 1967

141. Davis JO: What signals the kidney to release renin? Circ Res 28:301-306, 1971

142. Stein JH, Ferris TF: The physiology of renin. Arch Int Med 131:860-875, 1973

Refer to: Syphilis—Medical Staff Conference, University of California, San Francisco. West J Med 120:46-54, Jan 1974

Syphilis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *The topic for Medical Grand Rounds this morning is one of increasing importance to all physicians. We have asked Dr. Marcus Conant of the Department of Dermatology to discuss the great mimic, syphilis.*

DR. CONANT:† I would like to give you a historical and clinical review of syphilis and in so doing attempt to make two essential points. The first is that we are experiencing a pandemic of syphilis in the world today and that this pandemic is centered primarily in large metropolitan areas such as San Francisco. The incidence of venereal disease, and particularly syphilis, in this community is appalling. This University of California, San Francisco, is one of the largest medical centers in the country and is located in the midst of this epidemic. Yet it would appear that we are doing very little as an institution to assist the community in eradicating syphilis.

The second point that I would like to stress is that syphilis has continually changed in its clinical presentation since it was first described in the early 1500's, and it is continuing to change today. The classical disease that was described by de Villalobos and others back in the early 1500's is no longer seen. What de Villalobos described was an acute febrile disease that suddenly erupted in a community. Large numbers of victims were suddenly struck down with a great pox that spread rapidly over the patient, producing great morbidity and frequently causing death. The syphilis that we see today is far more insidious, frequently is discovered with no history of a chancre, and is often devoid of all but the mildest cutaneous eruption. More and more frequently, secondary syphilis is being misdiagnosed as hepatitis or mononucleosis.

In 1800, Lord Byron wrote a couplet more prophetic than poetic: "The smallpox has gone out of late, Perchance it will be followed by the great." It was not in Byron's time, however, but in ours that his prophecy was borne out. The reported incidence of syphilis in the United States was about 10,000 cases a year in the period 1920 to 1930. In the late 1930's the incidence began to climb, and during the early war years of the 1940's, the reported incidence reached about 35,000 cases a year.[1]

Penicillin was discovered in 1942, and follow-

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†Marcus A. Conant, MD, Assistant Clinical Professor, Department of Dermatology.

ing its introduction into the physician's armamentarium, the incidence of reported cases of infectious syphilis began to fall, decreasing from 35,000 in 1940 to approximately 2,000 in 1960. Then an amazing thing began to happen, for, while new and better antibiotics were being discovered, many of which are very effective in the treatment of infectious syphilis, the incidence of the disease began an exponential rise in early 1960 and continued this increase until, last year, more than 90,000 cases were reported.

There has been a lot of argument about these figures. Some have argued that this is only a reflection of population growth and better reporting. But if one plots a population growth curve against the exponential increase that we have seen with syphilis, the slope of the syphilis curve is certainly more acute than the population growth curve. It has also been argued that reporting today is better than it was forty years ago and that this accounts for the rapid increase that has been seen. Contact work conducted primarily by the U.S. Public Health Service is unquestionably better than it was forty years ago. But if you will recall that before 1940 patients with syphilis were treated with arsphenamine (Salvarsan®) or one of the heavy metal compounds and that they were generally treated in large medical centers over long periods, it becomes obvious that most of those cases were, in fact, reported to the local health authorities. Today, with penicillin readily available, a clinician can make a clinical diagnosis of syphilis, give the patient an injection of penicillin, and yet not report the case to the local authorities who would initiate the proper contact work. In his zeal to treat and care for his patient, the clinician often forgets that, for every case of syphilis he sees, there is another case from which his patient contracted the disease. The public health authorities estimate that only one out of ten to one out of fourteen cases of syphilis in this community are, in fact, reported to them. This, of course, means that the absolute number of cases of syphilis in our community may be ten times higher than that indicated by available figures. The incidence of primary and secondary syphilis in San Francisco rose from 209 reported cases in 1968 to 624 reported cases in 1971. If we compute national incidences by determining the number of cases per 100,000 persons, we arrive at a statistic of 12 cases of syphilis per 100,000 nationally and of 81 per 100,000 in San Francisco.

Numerous reasons have been cited as the primary cause for the increased incidence of syphilis observed in this country in the last ten years. These include promiscuity of the young, sexual experimentation, the birth control pill, increased incidence of homosexuality, changing moral standards, lack of public interest, poor physician training, lack of research funds, social crowding, and (so far as known incidence is concerned) better reporting of contacts. In all probability, no one factor has been responsible for this epidemic. Rather, the problem we now face has come from a concert of many of these factors.

Six Is a Shibboleth in the Stages of Syphilis

For those of you who have not thought much about syphilis for the last few years, let me quickly run through the classical stages of the disease[2] and introduce a concept that I think you will find useful. As to the stages of syphilis, think in terms of sixes. The reason for stressing this will become apparent in a moment. The classical chancre is a nonpainful, indurated, ulcerative lesion frequently located on the penis or cervix, and usually it is associated with regional lymphadenopathy. The lesion usually appears about six weeks after the patient is infected with the disease. The incubation period can be anything from four to ten weeks. The chancre, after it appears, will usually last for a period of from six days to two weeks, and usually after about the sixth day of its appearance the fluorescent treponemal antibody-absorbed (FTA-ABS) test becomes positive.[3] Usually, the Venereal Disease Research Laboratory test (VDRL) becomes positive about the seventh day. This means that the FTA generally becomes positive slightly before the VDRL; and so in the clinical evaluation of early syphilis, one should instruct the laboratory to run both tests, regardless of the reactivity of the VDRL. As you will recall, the chancre begins to disappear at the point that the VDRL becomes positive. This, of course, means that in evaluating an early chancre, the darkfield examination is the only way of making a positive diagnosis. As the chancre is beginning to disappear, the darkfield examination coupled with the VDRL and FTA will establish the diagnosis. A period now elapses between primary and secondary syphilis, and this time can be anything from six weeks to six months. During this period, the titer of the VDRL is rising very rapidly. Classically, a papulosquamous eruption then develops over the patient's entire body, with a papular syphilid of the palms and systemic symptoms including a

low-grade fever, lymphadenopathy, malaise, sore throat, and alopecia. The rash of secondary syphilis usually lasts for about six weeks and then begins to slowly disappear without treatment. Then a long latency period ensues. The latency period may last anywhere from 18 months to 12 years before the patient begins to show signs of tertiary syphilis. Six years is a convenient figure to remember.

History of a Lively Commerce

One way to assist you in making a diagnosis of syphilis is to review the history of the geographic spread of the disease which in itself is a fascinating study and gives an overall view of what has happened to it over the last five hundred years.[4] Syphilis was probably unknown in Europe and Northern Africa until 1493. There are some authorities who still argue that the disease did exist there before that time; but if it did, it existed only as a localized endemic disease and did not cause the epidemic disease that was seen after Columbus returned from the New World. Most medical historians feel that the disease was contracted in the Western Hemisphere from natives and brought back and introduced into southern Spain at the time of Columbus' return in 1493.

Columbus landed south of Seville and travelled to Seville with six Indians and six of his sailors and probably first introduced the disease into that town renowned for oranges, bullfights, and torrid love affairs. Queen Isabella and King Ferdinand were holding court in Barcelona, and so this party of famous adventurers travelled from Seville to Barcelona to present themselves at court. Now you must try to imagine the enthusiasm that greeted Columbus on his return. It was probably greater than the enthusiastic welcome which we gave our astronauts. Columbus had not only sailed away and returned from the edge of the world, but he could bring back natives and artifacts from a new and foreign culture. Unhappily, he also returned with a new disease. (At least in this country, we profited from an admonition which George Santayana has put into graceful words, that those who do not study history are destined to repeat it. When our astronauts returned from the moon, we did place them in an isolation chamber until it could be determined that they were free of any extraterrestrial disease.)

Columbus visited the court of Spain and was well entertained by the powerful and wealthy of the land. The powerful invited Columbus and his troops to their villas and tables, and young ladies bestowed their favors on these adventurous young men. Apparently, the disease spread rapidly and became endemic in southern Spain within a matter of months. A year later, Charles VIII of France was at war with Naples. Naples was held by the Holy Roman Empire and, of course, the Holy Roman Empire at that time included the Hapsburg Empire, Austria, Hungary, Italy, Spain, and Portugal. The city of Naples hired Spanish mercenaries to come and help them fight the King of France. The Spanish armies brought syphilis with them and shared it with the camp followers around Naples, who in turn shared it with the French, and soon the army of France began to show signs of the new disease. The French were successful in their campaign against Naples; but, unfortunately for France, typhus made its European political debut the night after the battle, and the French army was literally decimated before dawn. The French troops had to withdraw to France, taking with them few spoils of war and their newly-acquired disease. This was the period in history when France was expeditionary throughout Europe, and for the next fifty years, the French army spread the disease over the face of the land.

A Reverse Nationalism of Names

Each country named the disease for some other country. In Italy, it was known as "the French disease," in France as "the Italian disease," in England as "the Spanish disease." The first written mention of the disease was by the Diet of Worms in 1495. The Diet issued an edict saying that the disease (which it called *bösen Blattern,* "the evil pox") was infectious and that the patient should be isolated. The edict cautioned that no one should engage in sexual contact with the patient until after the disease had disappeared. This was, of course, before it was realized that the patients were still infectious during the early latent period.

Mercury was first used in 1497 and, of course, heavy metals were the treatment of choice from that time until the early 1940's.

Francisco Lopez de Villalobos wrote the first medical treatise on the disease in 1498. As I have mentioned, he described a disease quite different from that seen today. He said that the first symptoms were usually severe rheumatic pains, fol-

lowed by high fever with prostration and then a rapidly progressing eruption with draining sores over the entire body. The descriptions are more reminiscent of the pustular forms of syphilis than of the papulosquamous forms that are more commonly seen today. The disease was apparently quite catastrophic and spread rapidly through an entire town.

Hieronymus Fracastorius, in 1530, gave the disease the name that we still use. Fracastorius was a very famous Italian physician who practiced and taught in Verona. This was a period in history when the Reformation was challenging the Catholic Church and the Council of Trent was formed to launch the counter-reformation. Fracastorius was chosen by the Pope as the physician to the Council of Trent. An example of the classical Renaissance man, Fracastorius was not only physician and scientist but artist and writer as well, and he used the Renaissance approach to describe the evil pox. He took the famous story of a young shepherd boy who angered the gods and was then struck down by them in vengeance. In telling of the punishment visited on the shepherd, Fracastorius had the boy struck down by a loathsome disease which, described in poetic form, had all of the then recognized manifestations of syphilis. Of course, the name of the young shepherd was Syphilus.

Parenthetically it may be noted that an old wives' tale which has circulated for centuries has it that syphilis, or at least some venereal disease, is contracted from having sexual intercourse with sheep. Man, of course, is the only animal that can contract this disease, and there is no basis in fact for this misconception except that Fracastorius chose a shepherd boy as the hero of this story.

Forty-two years after Columbus returned to Spain, Ruy Diaz de Isla wrote his memoirs. The year was 1539, but de Isla recalled that he had been practicing in southern Spain at the time of Columbus' return and that he had seen some of the sailors from the ship. He recalled that the sailors did suffer from a pox that then rapidly spread throughout the country, and he called the disease "the serpentine disease," not because of its morphological appearance, but because, he said, it was the most loathsome disease he had ever seen. He also said that in his practice he had seen some 20,000 cases of syphilis, which means that he must have been seeing two or three cases a day.

The Four Plus Nonplus of Dr. Hunter

John Hunter was the first to try to debunk the idea that syphilis and gonorrhea had the same cause. In his classical experiment, Hunter took pus from a patient who had gonorrhea and innoculated himself with this material. Unfortunately, he picked the wrong patient, because the patient that he chose as his donor also had syphilis, and Hunter acquired both gonorrhea and syphilis. He died from the latter disease some twenty years later, and his experiment confused the issue for another 30 years. The Scottish physician Dr. Benjamin Bell finally did further experiments and showed that gonorrhea and syphilis were two completely distinct diseases. Dr. Bell did his work on medical students, so it would appear that going to medical school in those days was more perilous than it is today. At least our students do not acquire the disease in the classroom.

From Hunter's study the relevant point to today's clinicians is not to forget that the patient you see with gonorrhea may well have acquired syphilis at the same time, and in evaluating and treating the patient's gonorrhea one must also evaluate and, if necessary, treat for syphilis.

Charcot in 1874 described the gastric crisis of secondary syphilis and the destructive joint changes of tertiary lues. In 1890, Hutchinson described the classic triad of congenital syphilis—notched incisors, eighth nerve deafness, and interstitial keratitis. Two years later, Gene Fournier first proposed the concept of latency. Until then, it had been accepted that when patients recovered from the eruption of secondary syphilis, they had recovered from the disease. It was not known that the disease became latent for a period of six years or so only to resurface later as gummas, neurological lesions, and aortic aneurysms. Fournier's concept of latency was correct. Today, we divide the latent period into two intervals. Early latent syphilis is anytime within two years after the patient recovers from the secondary lesions of the disease. Late latent syphilis is anything more than two years after the secondary eruption.

Carl Landsteiner is a name that you all know from his work on isolating blood group antigens. It is now frequently forgotten that Landsteiner, in 1906, was the first to introduce the darkfield microscope for the detection of treponemes in syphilitic lesions. The same year, August von Wassermann, working with Albert Neisser for whom the gonococcus was named, introduced the

Figure 1.—Chancre

Figure 2.—Chancre of meatus

Figure 3.—Chancre of finger

Figure 4.—Anal chancre in child

Figure 5.—Chancre of lip simulating herpes simplex

Figure 6.—Macular syphilid

Figure 7.—Papulosquamous lesion of secondary syphilis

Figure 8.—Papulonodular lesion of secondary syphilis

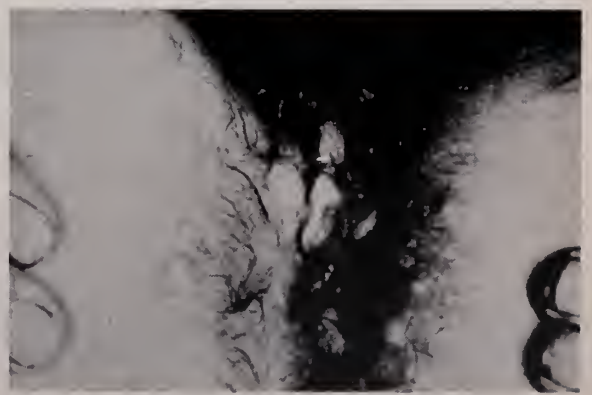


Figure 9.—Condylomata lata

Figure 10.—Lues maligna

Figure 11.—Annular syphilid

Figure 12.—Split papules

Figure 13.—Gumma, nose

Figure 14.—Gumma, breast

Figure 15.—Papulonodular syphilid

Figure 16.—Papulonodular syphilid

Figure 17.—Alopecia of beard

Figure 18.—Secondary syphilis, anal lesion

Figure 19.—Keratotic syphilid of tongue

first complement fixation test. Paul Ehrlich in 1910 introduced arsphenamine, also called Salvarsan® or 606, which of course was the main form of syphilitic therapy until penicillin was discovered by Fleming in 1943. Julius von Wagner-Jauregg, about 1917, introduced the concept of fever therapy.

A Key to Fever Therapy in an Old Report

It is of interest that when de Isla wrote his treatise on the serpentine disease in 1539, he observed that patients who had malaria, and high fevers from that disease, appeared not to get syphilis. Unfortunately, this observation was totally lost for the next 400 years. Von Wagner-Jauregg again discovered that if one elevates a patient's temperature to about 104°F for a time, Treponema pallidum are killed. Following von Wagner-Jauregg's work, treatment of patients in an electronic cabinet or by wrapping them in hot blankets was widely used in the treatment of syphilis from about 1920 until the mid 40's. One reason this classical treatment should be of interest to those in this audience is that Doctors Edward Levine, Norman Epstein and Francis Torrey of our Department of Dermatology used the treatment successfully in a number of patients, and the University of California, San Francisco, was one of the major institutions on the West Coast where fever therapy was used in the treatment of syphilis. All of this changed in 1943 with the introduction of penicillin, and many authorities felt that the young shepherd, Syphilus, had finally escaped further punishment from vengeful gods; but, unhappily, as I have mentioned, this has not been the case.

Let us look at some of the classical lesions of the disease. Figure 1 shows a classical indurated, ulcerated, nonpainful chancre such as is usually associated with lymphadenopathy. This lesion can be anywhere. It can present on the shaft or glans of the penis, on the mons pubis, labia, or cervix. More rarely, the lesion is discovered on the tongue or a tonsillar pillar, or a finger. Patients will frequently not seek medical attention because the ulcer is not painful and they cannot imagine that a nonpainful lesion can be harmful. The lesion seen in Figure 2 may cause some difficulty with urination. You may not find a large node with such lesions because lymph drainage is back to the periaortic nodes. However, on darkfield examination, as with all primary and secondary lesions of syphilis, the lesion will be teeming with treponemes. Figure 3 is a picture of a chancre on a finger, but I think that few of us in this room would think of syphilis as the first diagnosis. A giveaway may be the fact that the lesion is not painful and, of course, the patient will have a large axillary or an epitrochlear node. Perianal and anal lesions occur commonly in both males and females and even, (Figure 4) unfortunately, in children. The lesion shown in Figure 5 could be easily confused with herpes simplex. Even the large submandibular node seen here, which in this case is a syphilitic bubo, can also be seen with herpes. If the patient does not give a classical history of recurrent herpes simplex, a darkfield examination on this lesion is mandatory.

The Mimicry of Secondary Syphilis

The lesions of secondary syphilis provide a wide clinical spectrum and are a paradise for the morphological dermatologist. The disease in this stage can take on almost any appearance (Figure 6). In Figure 7 you see the rather classical papulosquamous lesions of secondary syphilis. Patients with this condition will usually tell you that they have mild sore throat and a little hoarseness. Frequently, they will have noted a mild upper respiratory tract infection. Many internists on seeing a patient with a mild evanescent rash, a little upper respiratory tract infection, malaise, and lymphadenopathy might well consider mononucleosis as their first diagnosis. Secondary syphilis must be considered in your differentiations, and a specimen for a VDRL test must be drawn. Papulosquamous lesions may be confused with pityriasis rosea or even psoriasis. The papulopustular form of syphilis is not seen very frequently today but is apparently the type of pox lesion that was described by de Villalobos and others in the early 1500's. Palmar and plantar lesions with hyperkeratotic papules are very common in secondary syphilis. One point that helps in clinical differentiation of pityriasis rosea from secondary syphilis is the fact that plantar and palmar lesions are rare in pityriasis rosea and common in syphilis. However, you should always get a VDRL test to confirm your clinical impression.

The papular nodular lesions in syphilis (Figure 8) may be slightly tender with pressure and usually the eruption does not itch. Condylomata lata (Figure 9) are easily confused with condylomata acuminata. Again, this is a lesion of sec-

ondary syphilis, and the patient will have a high VDRL titer. These lesions are teeming with treponemes, which can be easily recovered for darkfield examination.

The drier lesions on the body produce a greater problem, but frequently organisms can be demonstrated in these lesions if a saline sponge is used to prehydrate the lesion for ten to fifteen minutes. The top of the lesion is then lightly debrided with a dry swab, pressure is applied on the sides of the lesion, and sera is collected for examination.

We saw a young patient here some years ago who was suffering from a rare but well described variant of secondary syphilis which has been called lues maligna (Figure 10). In this condition, large ulcerative lesions are usually seen. The disease is one of late secondary lues and commonly lasts for weeks to months. The patient had consulted two or three physicians, who had not come to a correct diagnosis. He then became a recluse and turned to Christian Science. When the disease continued to spread, he came to this hospital where the proper diagnosis was made by Dr. D. A. Fisher, and the patient was treated with penicillin.

The annular lesions of secondary syphilis (Figure 11) are seen almost exclusively in black patients. If these lesions occur at the corner of the nose or the edge of the mouth, they are referred to as split papules (Figure 12). If you see such a lesion, syphilis is probably a much more likely diagnosis than cheilitis due to a vitamin deficiency. Figure 13 shows a tertiary lesion of syphilis destroying the nasal septum and Figure 14 shows a similar lesion on a breast. I think most clinicians would be far more concerned about carcinoma, but do not let your concern for that disease dull your diagnostic acumen to the point that you neglect to order a VDRL and FTA-ABS to rule out tertiary syphilis.

The pictures that you have just seen are some classical photographs of primary and secondary syphilis distributed by the Public Health Service. I would like to end this dissertation by showing you pictures from four or five cases that I have seen over the last year or two to indicate how we are seeing syphilis in this community today. The lesions seen in Figures 15 and 16 had been present for a few days and they itched slightly. The patient was concerned about scabies. As you see, the lesions have no scales such as appear in classical secondary syphilis. These small papulonodules were present over most of the body but particularly in the inguinal area and on the penis. The VDRL reaction was 1:64 and these are lesions of secondary syphilis.

Figure 17 shows the face of a young man who sought medical advice because of alopecia of the beard area. Most of us would immediately make a diagnosis of alopecia areata and advise the patient that little or nothing can be done to treat the condition. But the patient said in his history that at the time this loss of hair in the beard area had developed, he had begun to have an unusual, nonpruritic eruption on the chest, which he had attributed to a fungus infection. Examination revealed an erythematous macular eruption which could in fact have been confused with tinea versicolor. On the patient's penis, there was a small papulonodular lesion and the patient's VDRL reaction was 1:64.

Another patient had seen his family doctor for a lesion in the anal area which had been present for about two weeks. A diagnosis of hemorrhoids had been made and the patient had been advised to use phenylmercuric nitrate (Preparation H®). On examination a tender, ulcerative lesion with a large fissure running diagonally through the center was seen (Figure 18). Darkfield examination of the lesion was positive for syphilis, and one would certainly consider the diagnosis of primary syphilis, but on further examination a 3 to 4 mm papulonodular lesion was seen on the glans penis. The patient's VDRL was 1:64, and he too had secondary syphilis.

The next case presented a fascinating problem a few years back. The patient, a young man, consulted a physician because of lymphadenopathy. He was told that he had mononucleosis. A heterophile test was done, and the physician later reported to the patient that his case was most unusual because the result of the test was negative. The boy was treated conservatively, and when he did not improve he consulted another physician who also told him that he had mononucleosis. The second physician also ordered a heterophile test and he, too, reported to the patient that the test was negative. Finally, a keratotic lesion (Figure 19) developed on the patient's tongue. The lesion was quite firm and did not scrape off easily. The patient presented himself to the University of California emergency room, where a diagnosis of mononucleosis with thrush was made. For treatment of thrush he was referred to the dermatology clinic, and there a darkfield examination was done. This oral lesion was teeming with treponemes. The VDRL titer was high. The patient was

treated with penicillin. Here was a case of secondary syphilis misdiagnosed by three physicians as mononucleosis.

Two points I would have you keep in mind. The first is that syphilis is occurring in this community and that it is occurring with great frequency. The second is that the disease has slowly changed through the centuries and apparently is becoming more insidious and frequently obtuse in its initial presentation. Certainly, if any physicians in America have an opportunity to diagnose and treat syphilis, it is those of you seated in this audience this morning, and I hope for your sake and the sake of your patients that you do not miss this opportunity.

Trade and Generic Names of Drugs

Salvarsan® ..... Arsphenamine
Preparation H® ..... Phenylmercuric nitrate

REFERENCES

1. Syphilis—A Synopsis: Public Health Service Publication No. 1660, Washington, D.C., U.S. Government Printing Office, 1967
2. Syphilis and other Venereal Diseases: The Medical Clinics of North America. Philadelphia, Pa, W. B. Saunders Co, 1964
3. Escobar MR: Fluorescent antibody tests of syphilis using cerebrospinal fluid: Clinical correlation in 150 cases. Am J Clin Path 53:886-890, Jun 1970
4. Dennie CC: A History of Syphilis. Springfield, Ill, Charles C Thomas, 1962

Selection of Shoes for Growing Feet

With regard to shoes and footgear in the growing foot, the critical consideration is that the shoe fit properly. The shoe should be long enough to allow an adult thumb breadth between the end of the great toe and the end of the toe box of the shoe when the child is standing. It should also be wide enough so that, when the fifth metatarsal is pushed against the lateral edge of the upper part of the shoe, approximately 1/8th to 3/16th inch of slack can be felt to overlie the first metatarsal head on the medial side of the shoe. The heel should not ride up and down excessively as the child walks; and with regard to material, I think that soft leather or canvas shoes (such things as sneakers) are probably preferable to rigid counters and hard leathers. The box-toe style of shoe—that is to say, an *un*pointed shoe—is the only proper footgear at any age. More problems have been caused by high-heeled pumps with the pointed shoe, which was formerly popular among young women, than by any shoes made for children.

A question frequently asked of pediatricians or family practitioners is about the time when the baby should be given his first pair of shoes. There is no good evidence that shoes do anything for the feet other than protect them, and hence it probably makes no sense to buy shoes until protection from the cold ground or glass or rocks underfoot becomes essential. Walking barefoot in the house, or with a soft moccasin type of shoe, is probably best when the infant begins to walk. Elevated heels, that are currently in style, are not a good idea; but, by and large, American childrens' shoe styles are good. Another frequently asked question is whether high-top or low-top shoes are preferable. I think it really makes no difference from the standpoint of the foot. High lace-up shoes are harder for the baby to take off and hence probably are better for mama's back, but make very little difference to the development of the baby's foot. Normal toddlers do not have significantly weak ankles and do not need the support of a high-top shoe about the ankle.

—Elmer E. Specht, MD, *San Francisco*
Extracted from *Audio-Digest Pediatrics*, Vol. 19, No. 19, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Specialty Conference

Refer to: Connor JD, Buchta RM, DeGenaro F Jr, et al: Potpourri of adenoviral infections—Pediatric Grand Rounds, University of California, San Diego, and University Hospital of San Diego County (Specialty Conferences). West J Med 120:55-61, Jan 1974

Participants

JAMES D. CONNOR, MD
RICHARD M. BUCHTA, MD
FRANK DeGENARO, JR., MD
MARY ANN FLETCHER, MD
WILLIAM L. NYHAN, MD, PhD

Taken from the weekly Pediatric Grand Rounds held at the University Hospital of San Diego County, University of California, San Diego, School of Medicine, September 19, 1972

Potpourri of Adenoviral Infections

DR. CONNOR:* Our plan is to discuss human adenoviral infections, focusing particularly upon those that occur commonly in infants and children. To exemplify the kinds of problems encountered in patients who have adenoviral infections, we shall present three patients, each with a different type of clinical infection.

I shall first review some of the basic characteristics of the adenoviruses (Table 1) and the means used to isolate these agents in tissue culture and to identify them; and then I shall present some of the pathologic characteristics of adenoviral infection.

The adenoviruses are large deoxyribonucleic acid (DNA) viruses which are very stable under usual *in vivo* conditions, including the acidity of the stomach and the alkalinity of the intestine. Infectivity remains after long periods at body temperature. The unusual stability of these viruses seems to be provided by a very tight structure of surface or capsid protein and DNA in the inner core. Stability may be used to help identify a newly isolated agent which is being considered as a possible adenovirus. Lack of lipid in the outer coat or capsid of the virus also provides resistance to chemicals, such as chloroform and ether, which solubilize lipids. Hence, when lipid-containing viruses such as influenza or mumps viruses are exposed to ether or chloroform, the envelope containing lipid is disrupted and the virus becomes noninfectious.

Adenoviruses remain intact and infectious after passage through ether or chloroform. The ether or chloroform resistance test may be used, then, to differentiate adenoviruses from other large DNA viruses such as herpesvirus, all of the myxoviruses and others. It is a quick and convenient method for partial identification.

Another convenient test for identifying adenoviruses is based upon the presence in infected tissue cultures of large quantities of structural proteins which are found in all adenoviruses. Homogenates of infected tissue culture materials containing these proteins can be used as antigens to react against adenovirus antibody in a comple-

TABLE 1.—*Characteristics of Human Adenoviruses, Types 1-28*

Icosahedral structure (3-5-2 symmetry)
Large DNA virus (60-80 millimicrons)
Stable to heat (37°C and 24 hr.)
Stable to pH (pH 2-8)
Stable to ether (20% and 18 hr.)*
Common complement fixing antigen*
Characteristic cytopathic change (CPC)*
Characteristic intranuclear inclusion bodies*
Replication restricted to nucleus
Lack of pathogenicity for other animals

*Those characteristics commonly used in the diagnostic laboratory.

Reprint requests to: J. D. Connor, MD, Chief, Division of Pediatric Infectious Diseases, University of California, San Diego, School of Medicine, P.O. Box 109, La Jolla CA 92037.

*James D. Connor, MD, Chief, Division of Pediatric Infectious Diseases.

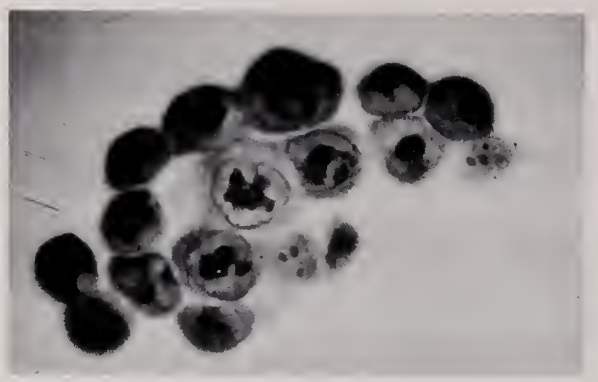


Figure 1.—Intranuclear inclusion bodies typical of adenovirus infection shown in cells infected in tissue culture.

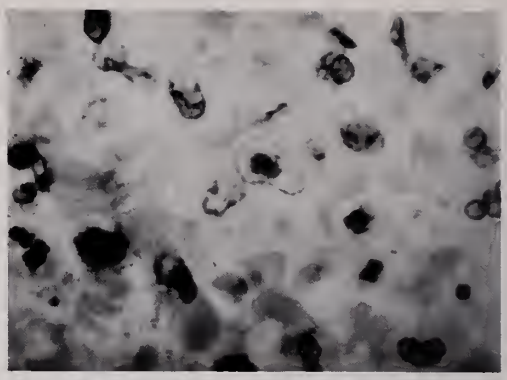


Figure 2.—Histologic appearance of the lung in an adenoviral infection. The characteristic cells are large and rounded and contain intranuclear inclusions.

ment fixation test, and adenovirus infected tissue cultures can be immediately identified in this way.

Adenovirus infection also produces a typical pattern of cytopathogenic change (CPC) both in *in vitro* cultivated cells and infected human tissues. These characteristic changes can be used presumptively to identify the virus infection in tissue culture. Infected cells become rounded, darkened and refractile. These cells aggregate into clumps, without cell fusion or syncytial cell development. The experienced virologic technician is able to use this type of characteristic CPC to identify the adenovirus infection in tissue culture with an accuracy of 90 percent or greater.

There is also a typical intranuclear inclusion body which may be observed in fixed and stained tissue culture cells which may be used as an aid in further identification (Figure 1). The inclusion body is a result of intranuclear replication of the virus and is composed of virus specific protein and nucleic acid as well as complete viral particles.

Other inclusion body producing viruses such as measles, cytomegalovirus, other herpesviruses and myxoviruses can be differentiated from the adenovirus by the characteristic appearance of the infected cell and the morphology of the inclusion body.

TABLE 2.—*Characteristic Human Adenoviral Infections*

	Type
URI	1,2,5,6 also 3,7,9,15
Febrile Pharyngitis	1,2,5,6 also 3,7,9,15
Pharyngo-conjunctival fever	3,7* (outbreaks); 14; 1,2,5,6, (sporadic)
Bronchopneumonia	7*,3,4,14,21,1,2
E.K.C.	8†
Follicular conjunctivitis	1,2,3,4,6,7,9,10,11, 15,16,17,20,22
Croup	1,2,5,6,7
Bronchiolitis	1,2,5,6,7

*In severe infections, adenovirus 7 was the most frequently isolated.

†Most severe types of ocular infection caused by type 8.

The structure of the adenovirus particle is that of an icosahedron, or twenty-sided figure, which is symmetrical in a 3-5-2 configuration. The outside, complex, large, protein subunits are known as capsomeres. In some areas, these are tied together into five subunits containing complexes known as pentons, and in others into six protein subunits known as hexons. These protein units and aggregates make up the antigen structure of the virus particle. Most of these proteins are produced in large amounts and there is a large excess of these antigens in infected cells. In fact, the majority of the structural proteins synthesized do not end up incorporated into complete virus particles. As a result, they are soluble in body fluids and are disseminated to other uninfected areas.

The human adenoviruses have a very restricted pathogenic effect in other animals. They do not cause clinically detectable infection in mice, hamsters, rats, rabbits or guinea pigs. Because of this species specificity, only human-derived tissue culture cells generally are effective in isolating adenoviruses from clinical material.

The histopathological findings that are associated with adenovirus infection in the lung are usually those of parenchymal tissue disorganization and necrosis. There is necrosis of bronchiolar membranes (necrotizing bronchiolitis) and characteristic large, rounded, dark cells containing intranuclear inclusion bodies (Figure 2). Around the infected bronchiole there is an accumulation of lymphocytes. The bronchiolar membrane may be stripped away completely and air entrapment or consolidation may ensue. The pathologic

Figure 3.—The eye of the first patient, illustrating a membrane over the palpebral conjunctiva.

changes of adenovirus infection in other organs are not nearly so distinct as those in the lung.

The spectrum of disease commonly caused by adenovirus infection is broad (Table 2). It includes the common cold, pharyngo-conjunctival fever, pharyngitis, membranous tonsillitis, laryngitis, croup, tracheobronchitis, pneumonia, gastroenteritis and keratoconjunctivitis. Other less well established conditions, which occur rarely, include meningoencephalitis, mesenteric adenitis, myocarditis and acute hemorrhagic cystitis.

The patients to be presented will include a variety of adenoviral infections. The diagnosis can often be challenging.

Membranous Conjunctivitis Due to Infection with Adenovirus Type 7

Dr. Buchta:* The patient was a nine-month-old boy who was first seen at the Naval Hospital, Camp Pendleton, California, because of a fever of two days' duration. Associated with the fever was rhinorrhea and swelling of the right eye. A diagnosis of acute purulent conjunctivitis was made, and treatment was started with sulfacetamide eye drops. After three days the parents returned the baby to the hospital since no improvement had been noted. A membrane was now present over the palpebral conjunctiva of the right eye.

The patient was the product of a normal pregnancy, labor and delivery. His growth and development had proceeded normally. He had had three documented DPT immunizations, the last of which was received at four months of age.

On physical examination the infant had a temperature of 99°, pulse rate of 120 and respirations of 20 per minute. The abnormal physical findings were confined to the face, where there was pronounced swelling of the right periorbital tissues with ecchymosis of both upper and lower lids (Figure 3). The palpebral conjunctiva was decidedly injected and there was a flat membrane over the palpebral conjunctiva and cul-de-sac. The bulbar conjunctiva was spared. The pupils were normal and there was no corneal ulceration. There were small preauricular and posterior auricular nodes bilaterally.

An incision was made into the conjunctival membrane (Figure 3) and a Gram-stained specimen of the material obtained showed club-shaped rods.

The possibility of a local infection with C. diphtheriae was entertained, and for this reason the infant was transferred to the Pediatric Infectious Disease Unit, University of California, San Diego School of Medicine. There the above physical findings and Gram stain reading were confirmed. However, in view of this child's complete immunization history it was considered that diphtheric conjunctivitis was an unlikely diagnosis.

Viral and bacterial cultures were obtained and treatment was started with ampicillin and with gantrisin eye drops. Result of a Schick test was negative, indicating immunity. On the following day neosporin ointment was added to the regimen. Over the first 48 hours after admission, there was gradual clearing of the conjunctivitis. Resolution of the membrane was slower and a small portion was still present on the lower palpebral conjunctiva after ten days.

The bacterial cultures revealed the presence of diphtheroids. Viral cultures were positive for adenovirus type 7, isolated from the right eye, nasopharynx, throat and rectum.

Two days after the infant was admitted to the hospital his mother developed conjunctivitis of her right eye without membrane formation. Bacterial and viral cultures of her eye exudate revealed no growth although a throat culture was positive for adenovirus type 7.

Adenoviral complement fixing antibody was present in the acute phase serum at a dilution of 1:32. Unfortunately this family moved from the area and the convalescent serum requested has not been sent. Nevertheless, the diagnosis of adenoviral infection has been established by culture.

Discussion

Membranous conjunctivitis is a clinical entity infrequently observed in pediatric practice. Included in the differential diagnosis are several

*Richard M. Buchta, MD, Instructor of Pediatrics.

etiologies such as (1) bacteria, (2) viruses, (3) fungi, (4) allergies, (5) toxins and (6) chemicals. Numerous bacteria, including C. diphtheriae, streptococcus, staphylococcus, pneumococcus, meningococcus and gonococcus, among others, have been found in this disease state. Rarely, Candida albicans, herpes and vaccinia are responsible. The observations in the present case permit the addition of adenovirus type 7 infection to the list.

Adenoviral infections of the eye usually present in three clinical syndromes: (1) Acute follicular conjunctivitis, (2) pharyngo-conjunctival fever and (3) epidemic keratoconjunctivitis. Acute follicular conjunctivitis is the most common type of adenoviral infection of the eye and the most benign. There are no systemic manifestations and the conjunctivitis clears in about ten days unless secondary bacterial infection is superimposed. All of the adenovirus serotypes have been implicated in this disease.

Pharyngo-conjunctival fever has most often been attributed to type 3 adenovirus although types 1, 4, 5, 6, 7 and 14 have also produced a similar clinical condition. This disease is characterized by the triad of fever, pharyngitis and follicular conjunctivitis, often associated with regional lymphadenopathy. Onset may be sudden or gradual with persistence of fever for about five days. Other systemic symptoms such as malaise, myalgia, headache and diarrhea may also occur. Typically there is a follicular conjunctivitis, with a pre-auricular lymphadenopathy in 85 percent of cases. Keratitis may be present but is usually mild. The duration of the illness is from three days to three weeks. Membrane formation has not previously been noted.

Epidemic keratoconjunctivitis is generally accepted to be caused by adenovirus type 8. Types 1, 2, 3, 7, 9 and 11 have, however, caused sporadic outbreaks. The clinical course of the typical type 8 infection may be characterized in the first stage by hyperemia and edema of the conjunctiva associated with photophobia and profuse tearing. This lasts for approximately 48 hours. Thereafter, a follicular conjunctivitis occurs which may lead to membrane formation. Around the seventh or eighth day, corneal infiltrates appear and the conjunctivitis rapidly disappears. The keratitis may persist for two or three months and occasionally for up to three years. Adenoviral particles have recently been demonstrated in corneal and conjunctival epithelium in this disease. Corneal erosion and conjunctival scarring after membrane formation are complications of severe epidemic keratoconjunctivitis. The membranes have been observed in some cases to last from one to twelve days. Topically applied steroids had no effect on a small number of patients treated during the acute and convalescent phase of their illness. However, beneficial results were reported in treating late corneal opacities. Dawson stated emphatically that "the number of patients who might benefit from steroid therapy represent a very small portion of all those infected with adenovirus type 8." This should apply to type 7 infections as well.

Since membranous conjunctivitis has the potential for permanent visual loss, it is essential to diagnose the etiological agent involved so that proper therapy may be instituted. In this unusually severe case with membrane formation, it was of great importance to make the diagnosis of viral infection and exclude other etiologic possibilities.

Abdominal Pain Leading to Laparotomy

Dr. DeGenaro:* The patient was a four-year-old caucasian girl with abdominal pain of two days' duration. During a visit to an emergency room two days before admission, a urinalysis revealed 10 to 15 white cells per high power field. No culture was taken. The patient was treated with gantrisin. Two days later the abdominal pain had become more persistent, cramping in nature and localized to the right lower quadrant. Anorexia and low grade fever had also developed, and she was admitted with a presumptive diagnosis of acute appendicitis. Physical examination on admission revealed diffuse abdominal tenderness, localized primarily to the right lower quadrant with minimal guarding. On rectal examination, there was tenderness in the right lower quadrant, but no palpable mass. The rest of the physical examination was normal except for the presence of tender bilateral anterior cervical lymph nodes.

Laboratory data: Hemoglobin 12.9 grams per 100 ml, leukocytes 6,100 cells per cu mm with 58 percent neutrophils, 37 percent lymphocytes, 4 percent monocytes and 1 percent eosinophils. Specific gravity of the urine was 1.035, the pH was 6, there were 2 to 3 leukocytes per high power field, and no protein, sugar or acetone.

At laparotomy that evening a small quantity of nonpurulent, free fluid was found in the

*Frank DeGenaro, Jr., MD, Assistant Professor of Pediatrics.

abdominal cavity. The appendix was easily located and was normal in appearance. The distal ileum and ileocecal valve were decidely edematous and thickened. Throughout the mesentery there were large firm rubbery nodes. The liver, spleen and kidneys were all normal in appearance. Biopsy specimens of the distal ileum and several nodes were taken and frozen sections showed heavy lymphocytic infiltration in the ileum and nodes, suggesting a diagnosis of lymphosarcoma.

A workup was begun which included a roentgenographic survey of the skeleton and chest, and a gastrointestinal series, intravenous pyelogram and bone marrow aspiration. All of these were within normal limits. The erythrocyte sedimentation rate was 54 mm in one hour. The antistreptolysin-O titer was less than 12 Todd units and a test for heterophil antibody was negative. The throat culture grew alpha streptococci and the stool culture S. aureus. Urine and blood cultures were sterile. Smears, sections and cultures of the lymph nodes for acid-fast and other bacteria and for fungi were negative.

Adenoviruses have been isolated from the viral cultures of the lymph node, stool, throat and nose. The virus from the lymph node was identified by neutralization as Type 1.

Complement fixing antibody titers to adenovirus were 1:256 and 1:512 in sera obtained on the fouth and eighteenth days respectively. Titers against mycoplasma, ornithosis, Q-fever, influenza A and B, parainfluenza 1, 2 and 3 and respiratory syncytial virus were all 1:8 or less in both specimens.

Epidemiological evaluation of the family and neighborhood revealed that a six-year-old male sibling had had mild abdominal pain with several loose stools and low-grade fever approximately one week before the onset of the patient's illness. In addition, one other child living nearby had similar symptoms. The week following the patient's illness, two other siblings in the family became ill with nonspecific complaints of upper respiratory infection and fever, and one of the two had mild abdominal pain.

Discussion

Two abdominal syndromes have been associated with adenovirus infections. These are mesenteric lymphadenitis and intussusception. In one study, reported in 1962, a group of 99 patients was divided into three groups according to diagnosis at laparotomy. The first 17 patients had acute idiopathic intussusception. Another 32 patients had nonspecific mesenteric lymphadenitis. The third group of 50 patients that had been subjected to laparotomy were diagnosed as having other conditions including intestinal obstruction and acute appendicitis. Mesenteric lymph node biopsy specimens were obtained from all of these patients and, in addition, acute and convalescent sera. Ten of the 17 patients (59 percent) with intussusception had concurrent or recent adenovirus infection as demonstrated by virus isolation or rising adenoviral antibody titers. In the group of 24 patients with mesenteric adenitis, 16 (67 percent) were demonstrated to have concurrent or recent adenovirus infections. In the third group (which may be considered a control, as neither abdominal syndrome was present) 38 were adequately studied and only 9 (24 percent) were found to have adenovirus infection. In addition, it was demonstrated that the peak incidence of intussusception and mesenteric adenitis occurred at a time when adenovirus was being isolated widely from other types of patients in the community, so that a temporal relationship with the presentation of their cases was demonstrated.

At Charity Hospital in New Orleans, the pathologic reports were reviewed on 189 cases of intussusception. It was found that in only 5 percent of them were there mechanical reasons for the intussusception, and in the remainder the condition was designated as idiopathic. On examination of the idiopathic cases, the ileocecal valve was inflamed or there were large Peyers patches and enlarged mesenteric lymph nodes in 47 percent, providing a site for intussusception. Adenovirus infection has been implicated in other cases of intussusception. A variety of organisms have been isolated in patients with mesenteric lymphadenitis. These include beta hemolytic streptococci, S. aureus, and, increasingly in the European literature, Yersinea organisms, particularly Yersinea enterocolitica and Yersinia pseudotuberculosis. Salmonella infections have been associated with mesenteric adenitis. Among the viruses, Coxsackie and ECHO viruses have been identified in patients with this disorder. It is interesting to note that in the present case the patient had pathologic changes in the distal ileum, cecum, ileocecal valve and in the mesenteric nodes. Pathologic change of this type has been widely observed in patients with intussusception or with mesenteric adenitis. It has not previously been considered in the differential diagnosis of lymphomatous neoplasm.

Figure 4.— Roentgenogram of the chest of the third patient, who had an adenoviral infection of the lungs.

Severe Respiratory Disease

DR. FLETCHER:* The patient was a ten-month-old white boy with a one-week history of fever, lethargy and vomiting. He had been admitted to the Naval Hospital, San Diego, three days earlier because of bilateral pneumonitis. Therapy was initiated with penicillin. A second x-ray film of the chest suggested progression. On the third day, the patient had a short, generalized convulsion, and lumbar puncture revealed 16 leukocytes, 75 percent lymphocytes, and normal glucose and protein. Blood gases, obtained shortly after the seizure while the patient was receiving nasal oxygen, showed that the pH was 7.11; the PaO_2 was 101 mm of mercury and $PaCO_2$ was 87 mm of mercury. Sodium bicarbonate was given to correct the pH to 7.36 and the $PaCO_2$ fell to 55 mm of mercury. The PaO_2 was then 72 mm on 30 percent oxygen. The patient was transferred to University Hospital.

The parents and both older siblings were in good general health, but they were noted, during the patient's stay in hospital, to have severe upper respiratory infections.

On physical examination temperature was 100.6°F, the pulse rate 125 and respirations 24 per minute. The blood pressure was 90/60 mm of mercury. There was a copious mucoid nasal discharge and mild pharyngeal erythema. The patient was having mild subcostal and intercostal retractions. There were diffuse rhonchi, mild rales and some wheezing throughout the chest, which was equal on both sides. The liver was palpable 2 cm below the right costal margin. The patient was quite sleepy. Muscle tone was decreased.

Admission laboratory studies were as follows: Hematocrit 27 percent, hemoglobin 8.6 grams per 100 ml, leukocytes 5,200 per cu mm, with 49 percent neutrophils, 46 percent lymphocytes, and 4 percent monocytes. The erythrocyte sedimentation rate was 4 mm in one hour. Results of urinalysis and electrolyte determinations were normal. The serum calcium was 7.4 mg and total serum protein was 4.9 grams per 100 ml. Blood gases with the patient in room air revealed a pH of 7.45 and PaO_2 of 42 and $PaCO_2$ of 39 mm of mercury. Oxygen therapy delivered by mist tent raised the PaO_2. The infant was also given a blood transfusion, ampicillin and oxacillin, and intensive chest physiotherapy. Kanamycin was added to the regimen after 24 hours. On the morning after admission, grand mal seizures developed. They remitted spontaneously. Immediately thereafter, ventilation was obviously inadequate and the infant was intubated. Blood gases revealed a pH of 7.14, PaO_2 56 and $PaCO_2$ 94 mm of mercury. Sodium bicarbonate was given intravenously and 40 percent O_2 was delivered. The pH was 7.47, PaO_2 was 53, $PaCO_2$ was 47 mm of mercury, and bicarbonate was 33 mEq per liter. An FiO_2 of 60 percent was required to maintain the PaO_2 at 73 mm of mercury or higher. Recurrent seizures requiring heavy sedation continued over the next several hours; but they resolved within eight hours, leaving a Todd's hemiparesis that resolved. Over the next several days, the infant continued to show an obstructive lung disease pattern (Figure 4) with prominent rhonchi and wheezing throughout both lung fields. There was only a minimal response to aminophyllin and epinephrine. Intensive chest physiotherapy and suctioning were helpful in clearing the heavy secretions. The patient was weaned from controlled to assisted ventilation after 24 hours. After 72 hours he was placed on blow-by, and 24 hours later the tube was removed.

Tracheal cultures yielded a heavy growth of adenovirus type 7. This information became available the fifth hospital day. The serum adenovirus CF titer was initially 1:64 and rose to greater than 1:512 in one week. At six weeks it was 1:256. Viral cultures of the cerebrospinal fluid and urine were negative. Bacteriologic cultures of the sputum revealed mixed flora of pseudomonas, citrobacter and S. aureus.

On discharge after 14 days, the infant still had coarse rhonchi over both lung fields and mild wheezing throughout. He had a moderate paroxysmal cough and minimal splenomegaly. For the

*Mary Ann Fletcher, MD, Chief Resident, Department of Pediatrics.

following month, the cough persisted, along with some wheezing. The infant's general well-being improved progressively.

Discussion

This infant presented many management problems, most of which have previously been described in association with severe adenovirus infections of the lung. When first seen he had diffuse bilateral pneumonia. The presence of rales as well as the wheezing and rhonchi, associated with a paroxysmal cough, without a whoop, suggest a process involving most of the respiratory tract with bronchial epithelial desquamation. He produced copious tracheal secretions that were not purulent on smear and yielded a light growth of mixed flora on culture.

The picture of respiratory failure that followed was one in which there was a defect in alveolar-capillary exchange requiring high ventilatory pressures and high oxygen concentrations to correct. Concurrently, there was an inability to exchange CO_2, requiring high rates and volumes of mechanical ventilation. It is important to note that the child's respirations rate never was greater than 40; it was thought that the obstructive lung disease might prevent him from breathing more rapidly. With CO_2 retained, acidosis developed, and decreased pulmonary flow resulted in further hypoxemia. As the patient's condition improved, the FiO_2 could be lowered and the pressure needed to deliver the preset volume became less as lung compliance improved.

A second problem was anemia. The hemoglobin was 8 grams per 100 ml. The peripheral smear showed microcytosis and moderate hypochromia but iron deficiency alone probably did not explain the anemia. Transfusion was carried out to improve the oxygen-carrying capacity. Nevertheless, the patient was able to manifest a reticulocytosis during convalescence in an appropriate period after iron therapy was started.

A third problem was central nervous system disease. The seizures were very severe. This undoubtedly contributed to the difficulty in maintaining adequate oxygenation. The PaO_2 was probably never low enough to account, primarily, for the seizures, although the low O_2 may have prolonged them or increased their severity. An abnormal electroencephalogram returned to normal within one week. The cerebrospinal fluid findings suggested a virus infection of the central nervous system. This type of complication has been more frequently found with adenovirus type 7 than with most other serotypes. The patient appears to have suffered no residua of these cerebral manifestations of the disease.

It was very helpful in the management of this patient to be able to document the adenovirus infection while he was ill. It explained a great deal about the course of this disease, and focused our attention on realistic modes of therapy for the pulmonary problem.

Summary

DR. NYHAN:* These patients illustrate the variety of presentation of serious illness due to adenoviruses. They illustrate particularly the use of the laboratory. In each instance the ability to provide a rapid specific viral diagnosis was important in the management of the patient. The first patient looked as though he could have had diphtheria, and examination of the initial smear furthered that impression. The second patient was thought to have an abdominal malignant disease when she was referred for study. The third had a life-threatening pulmonary infection. These experiences indicate how viral diagnosis has come of age in clinical practice.

---

*William L. Nyhan, MD, PhD, Professor and Chairman, Department of Pediatrics.

BIBLIOGRAPHY

Bell TM, Steyn JH: Viruses in lymph nodes of children with mesenteric adenitis and intussusception. Br Med J 5306:700-702, Sep 15, 1962

Brandt CD, et al: Infections in 18,000 infants and children in a controlled study of respiratory tract disease—II. Variation in adenovirus infections by year and season. Am J Epidemiol 95: 218-227, Aug 1971

Brandt CD, Kim HW, Vargosko AJ, et al: Infections in 18,000 infants and children in a controlled study of respiratory tract disease—I. Adenovirus pathogenicity in relation to serologic type and illness syndrome. Am J Epidemiol 90:484-500, May 1969

Dawson C, et al: Adenovirus type 8 infections in the United States—IV. Observations on the pathogenesis of lesions in severe eye disease. Arch Ophthamol 87:258-268, Mar 1972

Dawson C, Darrell R: Infections due to adenovirus type 8 in the United States—I. An outbreak of epidemic keratoconjunctivitis originating in a physician's office. N Engl J Med 268:1031-1038, May 9, 1963

Gold R, Wilt JD, Adhikari PK, et al: Adenoviral pneumonia and its complications in infancy and childhood. J Can Assoc Radiol 20:218-224, Dec 1969

Ginsberg HS: Identification of adenoviruses. Virology 18:312-319, 1962

Huebner RJ, Rowe WP: Adenoviruses as etiologic agents in conjunctivitis and keratoconjunctivitis. Am J Ophthamol 43:20-25, Apr 1957

Kawai K: Pathology and pathologic anatomy of adenovirus infection. Japan J Exp Med 29:359-368, 1959

Levy JL Jr, Lindes H: "Idiopathic" intussusception in infants. New Orleans So Med J 63:642-646, Jun 1970

Parrott RH, Rowe WP, et al: Outbreak of febrile pharyngitis and conjunctivitis associated with type 3 adenoidal-pharyngeal-conjunctival virus infection. N Engl J Med 251:1087-1090, Dec 1954

Pinkerton H, Carroll S: Fatal adenovirus pneumonia in infants. Am J Pathol 65:543-546, Dec 1971

Rowe WP, Huebner RJ, et al: Studies of the adenoidal-pharyngeal-conjunctival (APC) group of viruses. Am J Hyg 61:197-218, Mar 1955

Schmidt NJ, et al: Neutralizing, hemagglutination-inhibiting and group complement-fixing antibody responses in human adenovirus infections. J Immunol 97:64-74, 1966

Steen-Johnsen J, Orstavik I, Attramadal A: Severe illnesses due to adenovirus type 7 in children. Acta Paediat Scand 58:157-163, 1969

Important Advances in Clinical Medicine

Epitomes of Progress—Otolaryngology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Otolaryngology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Otolaryngology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Otolaryngology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, 731 Market St., San Francisco, CA 94103

Bone Grafts in Head and Neck Surgery

BONE GRAFTS can be divided for immunological purposes into three categories: (1) autografts, in which donor and recipient are the same; (2) homografts, in which both donor and recipient belong to the same species (including the subdivisions of allogenic, in which the donor is unrelated, and isogenic, in which the donor is closely related); and (3) heterografts, in which the donor and recipient are of different species.

Without exception, best results are still obtained with autografts, although poor remodeling, nonunion, resorption, and lack of osteogenesis occur in particular with solid, cortical implants, especially if intractable infection occurs. A notable advance has been the use of combination cancellate bone and marrow in preformed containers. The use of homograft bone in such a container is currently under investigation. Experimentation continues on best methods of preserving grafts, but to date, grafts which are expected to contain viable cells and promote osteogenesis have been autografts.

Reconstructive problems which require only an inert substance to maintain contour may utilize homograft or heterograft substances. An exception may be the recent successes of homograft ossicles, although wide investigative experience must still be obtained. With improving techniques of storage and alteration to remove potential immunologic characteristics of graft materials, the storage and use of homograft bone in partial or complete anatomic form appears to hold promising possibilities.

ALAN NAHUM, MD

REFERENCES

Boyne PJ: Transplantation, implantation, and grafts. Dent Clin North Am 15:433-453, Apr 1971

English GM, Hilyard VH, Hemenway WG, et al: Autograft and homograft incus transpositions in chronic otitis media. Laryngoscope 81:1434-1447, Sep 1971

Homografts in Otology

RESTORATION OF HEARING by homograft reconstruction of the ossicles, tympanic membrane and posterior osseous external canal defects is now a clinical reality. Middle ear and canal malformations or defects resulting from embryologic impropriety, infection, tumor or trauma may often be repaired by using homograft tissue.

Ear transplant material is removed from the donor within 24 hours of death. There is no donor

age limit although the donor should be free of infectious or malignant disease. The homograft tissue is procured by removing a portion of the temporal bone from the floor of the middle cranial fossa, which includes the middle ear and external auditory canal. Techniques for sterilizing, processing and preserving ear transplant tissue are established and such banked tissue is now available to ear surgeons.

The use of otologic homograft tissue is an attractive alternative because reconstruction using various types of plastics and metals has not been very successful. Extrusion of alloplastic materials in the middle ear is fairly common. The results of homograft ear operations during the past five years are most encouraging. There are no reports of extrusion or rejection of otologic homograft tissue.

MANSFIELD F. W. SMITH, MD

REFERENCES

Marquet J: Myringoplasty by eardrum transplantation. Laryngoscope 78:1329-1336, 1969

Smith MF, Proffitt SD, Shinn JB, et al: An otologic tissue bank. Trans Am Acad Ophthalmol Otolaryngol 76:134-141, Jan-Feb 1972

The Cytotoxic Test for Diagnosing Food Allergies

THERE HAVE BEEN a number of efforts to devise and utilize clinical methods for diagnosing food allergens: Rowe, Rinkel, Randolph, Lee and others have made contributions. Nevertheless laboratory methods seemed desirable due to the large amount of time used in the clinical methods, except for skin tests, which carry about 75 percent error. In 1956 Black proposed the use of the cytotoxic reaction for diagnosis of food allergy. This presumably was based on the experiments of Byron H. Wacksman.

We took up the test in 1957, gradually refining the technique so that it is now fairly reliable, the main remaining difficulties being the changing of the patients' diet and the fact that diagnoses are often multiple.

As we do it, the cytotoxic test consists of observing with the microscope the reactions of the blood cells (principally the activity of the neutrophils) to the food extracts in the presence of the patient's serum. All glassware which comes in contact with blood cells must be chemically clean and "silicated." Known accurate amounts of food extracts are used (0.1 mg of the powder per ml of pyrogen-free water overnight, then decanted and further diluted). Rings of vaseline the size of the coverslips are put three per slide to hold (1) the food extract; (2) the cells and serum, and (3) the coverslips. After an hour the cells are observed and the results recorded for each food.

After 15 years of use on almost 5,000 patients, and 250,000 individual tests, many and even some spectacular cures have been accomplished.

WILLIAM T. K. BRYAN, MD

REFERENCES

Bryan WTK, Bryan MP: The application of *in vitro* cytotoxic reactions to clinical diagnosis of food allergy. Laryngoscope 70: 810-824, Jun 1960

Bryan WTK, Bryan MP: Cytotoxic reactions in the diagnosis of food allergy. Laryngoscope 79:1453, Aug 1969

Acupuncture and Deafness

INFORMAL CLAIMS from China during the past two years have engendered considerable enthusiasm among patients for using acupuncture to treat sensorineural hearing losses. Experience in the United States is quite limited but of the several attempts at treatment by persons generally recognized as experienced acupuncturists, none have been successful when documented before and after by audiograms. Thus, while we can in no way state with certainty that acupuncture does not help deafness, the present evidence is negative.

It has been argued that such failures probably result from the use of the more traditional acupuncture points instead of newer ones discovered by China's Barefoot Doctors. They may be correct, but since one of these new points requires that a needle be inserted between C_1 and C_2 to a depth of 3 to 4 inches, it probably will be a long time indeed before practitioners of a more conservative bent find out.

F. BLAIR SIMMONS, MD

Diagnostic Uses of Immunoglobulins

OTOLARYNGOLOGISTS AND IMMUNOLOGISTS are investigating the presence, quantity, and function of immunoglobulins in the respiratory tract. These immunoproteins, IgG, IgA, IgM, IgD and IgE, are part of the gamma and beta fractions of serum and are also present on mucous membrane surfaces and in various body fluids. The technique most commonly used to quantitate these immunoglobulins (except IgE) is termed "single radial diffusion," implying incorporation of a monospecific antibody in the agar used for immunodiffusion studies; and serum levels of the immunoglobulins have been determined throughout the human life span. By varying antibody concentration in

the agar, very low levels of the immunglobulins can be measured routinely, and normal ranges of these proteins in certain body fluids such as nasal secretions have been established. An elevated serum IgM or IgG often signifies a response to an infection. IgE serum elevation may reflect an allergic disorder. IgA serum levels also may vary with host response to infection; but more important, IgA is the major or only immunoglobulin found in respiratory secretions. Individual and circadian variations of respiratory IgA levels have been documented, and this variation may play a role in susceptibility to infection, since a decrease or absence of any immunoglobulin can be associated with increased incidence of infection.

The Ig levels cannot be used alone for a diagnosis of any one disease—except the dysgammaglobulinemias—but may be useful in connection with history, physical examination, and other tests in determining the overall ability of the individual to handle infections.

STEBBINS B. CHANDOR, MD

REFERENCES

Buckley CE, Dorsey FC: Serum immunoglobulin levels throughout the life span of healthy man. Ann Intern Med 75:673-682, Nov 1971

Hughes EC, Johnson RL: Circadian and interpersonal variability of IgA in nasal secretions. Ann Otol Rhinol Laryngol 82: 216-223, 1973

Tomasi TB, Grey HM: Structure and function of immunoglobulin A. Progr Allergy 16:81-213, 1972

Bell's Palsy (Facial Paralysis)

THE DIAGNOSIS Bell's palsy implies, by definition, a non-specific involvement of the peripheral component of the seventh cranial nerve (facial nerve) with paralysis of structures innervated by the facial nerve.

The possibility of a systemic cause must always be considered and an evaluation by the generalist with medical studies as necessary should be performed.

If paralysis is on the basis of truly non-specific cause, medical management is in order. Treatment other than that is supportative with special attention to the eye to prevent corneal disease.

If the patient is seen early (preferably within 48 to 72 hours) steroids are the drug of choice.

Ninety percent of patients will recover spontaneously within three to six weeks. The remaining 10 percent will be left with a residual paresis or paralysis.

Special studies to predict who these 5 percent will be have been advocated and surgical intervention recommended. The studies consist of electrical studies for measurement of electrical nerve potentials.

Responsibility of management and treatment must be that of the primary physician, with consultation for those patients who do not respond to medical management.

SEYMOUR J. BROCKMAN, MD

REFERENCE

Adour KK, Wingerd J, Bell DN, et al: Prednisone treatment for idiopathic facial paralysis (Bell's Palsy). N Engl J Med 287: 1268-1272, 1972

Some Aspects of Dizziness

THE SENSE OF MOVEMENT (subjective vertigo) or the actual illusion of objects moving (objective vertigo) is a strong indication that the vestibular system is involved in the abnormality. On the other hand, unsteadiness, not as neatly defined as true vertigo, is not commonly related to the vestibular system. An otoneurologic evaluation of the patient complaining of vertigo necessarily includes a detailed history regarding: (1) the onset of the symptoms, (2) their character, duration, and mode of cessation, (3) whether they are single episodes or repeated, and (4) associated symptoms such as tinnitus, hearing loss, syncope, and palpitations. The examination itself must include evaluation of the cranial nerves, extraocular movements, cerebellar tests (including Romberg, modified Romberg, and pastpointing), tests for dysdiadochokinesis, vestibulospinal tract tests (such as position maintenance of extended arms with eyes closed), and electronystagmographic (ENG) analysis of eye movements. The electronystagmographic analysis of the eye movements should include: (1) *pendular tracking,* which can give evidence of abnormalities at the level of the oculomotor nuclei, (2) *calibration,* which not only allows quantitation of the ENG tracings but its qualitative pattern can give clues as to a peripheral or central nature of the disorder, (3) *optokinetic stimulation* which when recorded as an isolated abnormality is supportive of a cortical lesion, and (4) *positional testing* with particular attention to latency of nystagmus, associated vertigo, and the duration of the positionally provoked nystagmus for more than two minutes. *Rotational testing* is not routinely used in many laboratories but holds promise in the future perhaps even in differentiating between sites of peripheral lesions. *Caloric testing* using the Hallpike method is usually modified so that electronystagmographic analysis is obtainable with stimulation and recording in darkness and with

eyes closed, which allows the examiner to look for several types of abnormal responses. Among these would be a *canal paresis,* that is, where stimulation of one ear results in less vigorous nystagmus regardless of temperature of irrigant (7° above and 7° below body temperature); *directional preponderance,* which is a tendency, regardless of which ear is irrigated or what temperature is used, for nystagmus to be more vigorous in one direction (generally considered as a latent spontaneous nystagmus); *dysrhythmia,* which is an irregular nystagmus pattern usually indicative of cerebellar nuclei involvement; *perverted nystagmus,* which is nystagmus occurring in a direction other than that at the plane of the semicircular canal stimulated—that is, vertical nystagmus elicited at the time of horizontal canal stimulation consistent with a brain stem lesion; and *provoked nystagmus,* which, regardless of stimulus used, is always in the same direction (considered a provoked latent paretic nystagmus).

The above findings from an otoneurological evaluation coupled with the history and any other extension of the neurologic examination, laboratory, or x-ray findings, as well as audiometric testing, should allow differentiation of the disorder on a given patient. It is often convenient to use classical Meniere's disease as a point of reference in differentiating between the many types of disorders.

ROBERT I. KOHUT, MD

REFERENCES

Paparella MM: The dizzy patient. Postgrad Med 52:97-102, Aug 1972

Atkinson M: Otogenous cerebellar abscess. Ann Otol Rhinol Laryngol 40:1020, 1938

Henriksson N: A Synopsis of the Vestibular System. Monograph issued by Sandoz AG, Basle, Switzerland

Evaluation of the Dizzy Patient

FEW PROBLEMS presented to physicians of all disciplines are more perplexing than the "dizzy patient." Fortunately the majority of the disorders of the vestibular system are self-limiting. Most patients are initially treated symptomatically and it is only when symptoms persist that more thorough evaluation and referrals to a neurologist or otolaryngologist are made.

Even after extensive neurotological workup a definitive diagnosis may prove elusive because of the purely subjective nature of the tests of the vestibular function. Some neurotologists, either through long experience or deep insight, can sense with great accuracy the nature of the problem. For most physicians without extensive experience the results of the primitive tests that have been commonly performed do not provide sufficient information to make a correct diagnosis.

Electronystagmography (ENG) has achieved relatively widespread acceptance and it provides permanent documentation of spontaneous, positional and induced nystagmus. By documenting the response in the dark, it also is of value in demonstrating latent spontaneous nystagmus that cannot be detected with the patient's eyes open in a lighted room.

The current application of modern technology for inducing vestibular nystagmus (the new rotating tables) and the analysis of the voluminous ENG recorded responses by utilization of computer techniques, offer great promise for significant improvement in neurotological assessment. These techniques, developed in the animal laboratories, are now being applied to humans and are providing quantitative measurements of vestibular function in health and in disease.

PAUL H. WARD, MD

REFERENCES

Blach FO, Hemenway G: Electronystagmography (ENG) in vestibular testing. Eye Ear Nose Throat Mon 51:415-421, Nov 1972

Honrubia V, Katz R, Strelioff D, et al: Computer analysis of induced vestibular and optokinetic nystagmus. Ann Otol Rhinol Laryngol 80 Supplement 3:34-42, Dec 1971

Recent Advances in Differential Diagnosis of Hearing Problems

STANDARD PURE TONE and speech audiometric tests provide considerable information to otologists regarding uncomplicated middle ear or cochlear disease. Special diagnostic problems occur when responses to bone-conducted sound are nearly equivalent to air-conducted sound or when there is no consistency between the medical examination and the test results. Conditions such as otosclerosis, discontinuity and lateral fixation present a problem in differential diagnosis. With the advent of impedance audiometry, more precise information regarding the site of disease is available. Impedance tests describe (1) the mobility of the ear-drum, (2) the resistance of the moveable structures of the middle ear and (3) the presence or absence of the stapedial muscle reflex. These measurements can be taken in children as well as adults and may be of particular advantage to the school audiologist in identifying and referring children with otitis media that is not demonstrated by screening audiometry.

Hearing impairments may be designated as

sensori-neural or cochlear on the basis of the pure tone audiogram. This, however, does not describe the site of lesion other than to exclude middle or outer ear involvement. Retrocochlear lesions may occur at any point beyond the cochlea on the auditory pathways such as the 8th nerve, brain stem or auditory cortex. Various audiometric tests have been designed to differentiate between these pathologic conditions. Each presents a specific listening task which increases in difficulty. Otologists and audiologists have been encouraged by finding that there is a high correlation between these clinical tests results and the medical-surgical findings.

SEYMOUR J. BROCKMAN, MD

REFERENCES

Smith BB, Resnick DM: An auditory test for assessing brain stem integrity. Preliminary report. Laryngoscope 82:414-424, Mar 1972

Berlin C: Dichotic speech perception. An interpretation of right ear advantage and temporal offset effects. J Acoust Soc Am 53, Mar 1973

Jerger J: Clinical experience with impedance audiometry. Arch Otolaryngol 92:311-324, 1970

A Protocol for Evaluating Dizziness

A PROTOCOL has been established for the evaluation of a dizzy patient when there is any suggestion that the dizziness may be related to the inner ear. This protocol includes hearing tests, vestibular tests and x-rays of the inner ear. If these tests fail to show an otologic reason for the dizziness, then it is suggested that the patient have a five-hour glucose tolerance test, thyroid studies, FTA/Abs studies and, in some cases, an allergic evaluation. These studies will often give a clue to a treatable cause of dizziness.

WILLIAM F. HOUSE, MD

REFERENCES

Sheehy JL: The neuro-otologic evaluation. Arch Otolaryngol 88: 592-597, 1968

Powers HP, House WF: The dizzy patient—allergic aspect. Laryngoscope 79:1330-1339, 1969

The Significance of Post-Irradiation Edema of the Larynx

VARIABLE DEGREES of laryngeal edema often accompany curative dose, full course radiation therapy for cancer of the larynx. This edema usually subsides within a month or two. However, persistence of significant edema of the larynx beyond six months after completion of radiation therapy makes careful inspection and evaluation of the larynx difficult. A thorough search for tumor in such cases appears warranted. In 11 of our 14 most recent cases of "persistent edema," residual or recurrence eventually was proved to be present.

The edema is believed to be secondary to increased vascular permeability and obstruction of the small veins and lymph channels from hyaline degeneration of their walls. These radiation changes facilitate the obstruction to the passage of tumor cells through the lymphatic channels.

Less likely factors that may be responsible for "persistent postradiation edema" are previous laryngeal operation, infection, and perichondritis. Keeping the delayed development of edematous larynx under observation until tumor manifestations are clinically apparent diminishes the chance for curative operation. Diligence is called for when confronted with the diagnostic dilemma of "delayed edema." When evaluating such a patient, repeated biopsy, then exploration via laryngofissure are indicated in order to confirm the high diagnostic probability of residual or recurrent carcinoma.

PAUL H. WARD, MD

REFERENCES

Calcaterra TC, Stern F, Ward PH: Dilemma of delayed radiation injury of the larynx. Ann Otol Rhinol Laryngol 81:501-507, Aug 1972

Manara G: Histological changes of the human larynx irradiated with various technical therapeutic methods. Arch Ital Otol 79: 596-635, 1968

ADVISORY PANEL TO THE SECTION ON OTOLARYNGOLOGY

HERBERT DEDO, MD, *Chairman, San Francisco*

RICHARD GOODE, MD
CMA Section on Otolaryngology
Chairman
Stanford University

WILLIAM SIMPSON, MD
CMA Section on Otolaryngology
Secretary
Los Angeles

MANSFIELD SMITH, MD
CMA Section on Otolaryngology
Assistant Secretary
San Jose

ROBERT ROWE, MD
Loma Linda University

F. BLAIR SIMMONS, MD
Stanford University

LESLIE BERNSTEIN, MD
University of California, Davis

HOWARD HOUSE, MD
Los Angeles

ROBERT I. KOHUT, MD
University of California, Irvine
California College of Medicine

PAUL H. WARD, MD
University of California, Los Angeles

ALAN NAHUM, MD
University of California, San Diego

FRANCIS A. SOOY, MD
University of California, San Francisco

ALDEN H. MILLER, MD
University of Southern California
Los Angeles

SEYMOUR BROCKMAN, MD
CMA Scientific Board

DALE TIPTON, MD
San Francisco

MAURICE SCHIFF, MD
La Jolla

EDITORIAL

A Voice for Medicine in the West

THE WESTERN JOURNAL OF MEDICINE is being published by the California Medical Association as a voice for medicine in the West. It has been more than five years since the Council of the association directed the editors of CALIFORNIA MEDICINE to point toward the publication of a truly regional medical journal. The need for such a journal is obvious enough, and it has now come into being.

THE WESTERN JOURNAL OF MEDICINE is not really a new journal. Rather it is a natural outgrowth of a distinguished predecessor, CALIFORNIA MEDICINE, which felt that there was a larger job to be done. The three western coastal states have ten schools of medicine, and their medical associations have proven records of innovation and successful accomplishment. The vitality and achievements in science, education and practice which are the hallmarks of medicine in the western United States now need a stronger presence in the medical literature which records and shares advances and progress with the medical community in the nation and indeed the world. THE WESTERN JOURNAL OF MEDICINE hopes to give medicine in the West this presence and this recognition.

The opportunity is great and there is much to be done. The editors cannot do it alone. We are proud of the new Editorial Board. But we need and solicit the help of the medical community, the medical associations, the medical schools, the allied health professions, and especially physicians and physicians-to-be in research, academia, practice, and in the economics and politics of medical care. With the kind of help that should be available in this virile and vital region of the United States, THE WESTERN JOURNAL OF MEDICINE should indeed become a voice for medicine in the West. Let us do what needs to be done—together.

The Ubiquitous Adenovirus

IN THE MORE THAN 20 years since it was first isolated, the adenovirus has established a number of virologic firsts: the first agent to be isolated from tissue explants;[1] the first of the "new" viral agents to be harnessed into an effective virus vaccine;[2] the first viral agents isolated from humans capable of producing a tumor in animals;[3] and the first viral agent responsible for urinary tract disease.[4] A special conference entitled "Potpourri of Adenoviral Infection" published elsewhere in this journal therefore seems appropriate and worthy of additional comment.

It was in 1953 that adenovirus was isolated from tissue explants and from patients with respiratory illness.[1] Thus adenovirus isolation was an early, important clinical result from the momentous discovery of Enders, Weller and Robbins that viruses may easily be propagated in culture cell lines—a discovery which led to numerous scientific contributions and opened the door to the golden age of virology.

The adenovirus was soon found to be the etiologic agent for a variety of clinical syndromes. An important contribution in those early years was the discovery that acute respiratory disease (ARD), a common illness among military recruits, was caused by adenoviruses.[5] While this important etiologic and epidemiologic work was going on, concurrent work in the laboratory identified their biologic, physicochemical and immunologic properties. It was this information which made it possible to characterize human adenoviruses into 31 distinct immunological types. It was soon discovered, however, there was a common immunologic protein in all of these adenoviruses which made possible species identification on the basis of a simple complement fixation test.

Much of the early enthusiasm and intensive work on adenoviruses was based on the assump-

tion that these agents were responsible for a large percentage of respiratory disease in the general population just as in the case of military recruits. Therefore, isolation and characterization of these agents were followed in short order by the production of an effective adenoviral vaccine.[2] With further investigation, however, it became apparent that adenoviruses were not responsible for the bulk of respiratory illness in the civilian population. Data from a variety of sources established the fact that adenoviruses were probably responsible for no more than 5 percent of respiratory illness in the non-military population.[6] In essence, this left us with a vaccine in search of a disease—a true mark of an affluent society. The appreciation of differences in disease dynamics in different population groups was an important lesson which was not forgotten in subsequent infectious disease investigations.

Despite the fact the adenoviruses play only a small role in acute respiratory diseases in the civilian population, they are responsible for a wide variety of diseases involving many organ systems. These agents are frequently associated with tonsillopharyngitis or follicular conjunctivitis, which are mild infections. On occasion, however, adenoviruses may cause serious disease. Two of the cases discussed by Connor and his associates in the adenoviral conference emphasize this point. One case was that of a nine-month-old boy who had severe membranous conjunctivitis caused by adenovirus type 7. The second case was that of a ten-month-old infant with severe bilateral bronchopneumonia complicated by encephalitis. In this case, adenovirus type 7 was isolated from a tracheal specimen. Since both of these diseases can be caused by a variety of bacterial agents as well as by other viral agents, it is important to establish a diagnosis as early as possible so that appropriate therapy can be instituted, specifically with antibiotics in instances of bacterial infections. On the other hand, the complications and futility of antibiotic therapy can be avoided if one can with assurance establish a viral cause for a specific clinical entity.

The cases also serve to highlight some of the problems that still confront us with the diagnosis and treatment of adenoviral infection. Great strides have been made recently in facilitating rapid identification of a variety of viral agents. For example, the use of fluorescent antibodies makes it possible to establish, in a matter of hours, a diagnosis of herpes simplex and zoster infection, rabies or smallpox. However, there is still a need to develop inexpensive, rapid, simple and reliable diagnostic procedures that can be performed in most hospital laboratories for many viral agents, including adenoviruses. In addition, there is a need for specific therapy against viral agents, including adenoviruses, which are responsible for life-threatening illnesses. This assumes greater importance when one realizes that in addition to causing acute debilitating disease, with its concurrent morbidity and mortality, permanent sequelae may result from adenoviral infections, particularly in children under two years of age. For example, there are three recent reports involving almost a hundred infants and children infected with adenovirus type 7 or 21.[7-9] Disease resulted in death in about 6 percent of the patients. Lung fibrosis or segmental obstructive disease was noted in 25 percent of survivors while 16 percent had residual bronchiectasis. While these cases occurred during epidemics, sporadic adenoviral illness may also cause serious disease. We have recently seen an 18-month-old child with such an acute illness caused by adenovirus type 7 infection. This child was in hospital for 27 days and was near death during the height of her illness. Even ten months after discharge from the hospital this child was still dyspneic and had evidence of bronchiectasis and unresolved pulmonary infiltrates.

The association of certain types of adenoviral infections with serious illness in infants leads perhaps to a reconsideration of the usefulness of adenoviral vaccine as a preventive measure against these diseases. The introduction of the first adenovirus vaccine was premature. Work with a variety of other viral vaccines over the past ten to fifteen years has demonstrated the extreme caution that must be exercised in vaccine development. Should a virus selected for a vaccine be attenuated or inactivated? What is the best route of administration? What are the untoward effects, short term and long term? Can we arrive at a risk:benefit ratio from the use of this vaccine?

It is clear that these and other questions must be answered for every viral vaccine individually. Principles that have been learned from one viral vaccine may not be applicable to another. For example, inactive poliomyelitis virus vaccine is effective and safe. Inactive measles vaccine and respiratory syncytial virus vaccine stimulate antibody production but may be associated with an exaggerated clinical response when the vaccinate makes contact with the wild virus.

Experimental trials utilizing attenuated adenovirus vaccine types 4 and 7 are under way in the military.[10] The vaccine, administered orally in an enteric coated capsule, produces protective antibody. Administering enteric coated material to infants below two years of age presents one of the immediate problems that must be considered. In any case, it is clear that a great deal of thought and work must take place before an adenoviral vaccine is introduced for general use.

Another clinical aspect of respiratory adenoviral infection type 1 and type 5 is worthy of note. Recent evidence suggests these viruses may be primary etiologic agents or co-conspirators in producing the whooping cough syndrome. Precise definition of adenoviruses in this syndrome awaits further epidemiologic and experimental data.[11]

The small percentage of clinically apparent adenoviral respiratory disease may give the impression that we rarely encounter this agent. This is not true. The ubiquitousness of the adenoviruses is attested by the fact that 50 to 70 percent of infants inherit transplacental adenoviral antibodies.[6] This demonstrates that a large percentage of people have been exposed before the child-bearing age. If respiratory disease does not account for this exposure, we must look to subclinical infection or other clinical manifestations of adenoviruses as the antigenic stimulus for antibodies found in a great portion of the population. Subclinical infections undoubtedly occur and the manifestation of adenoviral infection in organ systems other than respiratory or ophthalmologic has been amply documented.

Another and more recently recognized facet of adenoviral disease involves infection of the mesenteric lymph nodes. Mesenteric lymphadenitis may be difficult to differentiate from acute appendicitis. More important, enlarged mesenteric nodes or enlarged Peyer's patches of the ileum may be due to adenovirus infection. Recent studies have suggested this mesenteric node inflammation and enlargement or ileocecal valve inflammation may result in intussusception in a number of cases which have previously been designated as "idiopathic."[12]

A fascinating aspect of mesenteric lymph gland involvement was described in one of the cases presented in the current adenoviral conference reported elsewhere in these pages.[5] The character of the lymph nodes on exploratory laparotomy of a four-year-old child suggested a lymphoproliferative disease rather than a primary inflammatory illness. Cultures from a variety of orifices and the lymph node yielded organisms ultimately identified as adenovirus type 1. The potential of adenovirus for stimulating tissue proliferation recalls the observations of Huebner.[3] In 1962 he produced sarcomas by inoculating adenoviruses into the cheek-pouches of hamsters. Production of these tumors involved adenoviral types not usually associated with human disease. Two years later Girardi induced sarcomas by use of adenovirus type 7, a common human pathogen.[13] A number of investigations that followed were unable to incriminate adenovirus in human oncologic disease. Most of the studies involved an unsuccessful attempt to isolate the viral agent from tumor extracts. These results are not unexpected, since adenoviral tumors produced in experimental animals do not yield infectious virus. However, as investigations with more sophisticated techniques are undertaken it may be found that the last chapter of adenoviral involvement in human tumors has not yet been written.

The ubiquitous adenovirus has also been incriminated in urinary tract disease. Hemorrhagic cystitis has been associated with adenovirus type 11.[4] Indeed, it is the only viral agent to date definitely associated with disease in this organ system.

The investigations over the past 20 years have incriminated adenovirus as an etiologic agent of a number of diseases. They have also provided provocative inquiries into oncologenic properties of viral agents. Although many of the infections with which adenoviruses are associated are mild, on occasion they may be the etiologic agents of serious illness with significant morbidity and mortality. It is doubtful that we have heard the last of the disease-producing capabilities of the adenoviruses.

HENRY R. SHINEFIELD, MD
Chief, Department of Pediatrics
Kaiser-Permanente Medical Center
Clinical Professor, Department of Pediatrics
University of California Medical Center
San Francisco

REFERENCES

1. Rowe, WP, Huebner RJ, Gilmore LW, et al: Isolation of a cytopathogenic agent from human adenoids undergoing spontaneous degeneration in tissue culture. Proc Soc Exp Biol Med 84: 570-573, 1953

2. Huebner RJ, Bell JA, Rowe WP, et al: Studies of adenoidal-pharyngeal-conjunctival vaccines in volunteers. JAMA 159:986-989, 1955

3. Huebner RJ, Rowe WP, Lane WT: Oncogenic effects in hamsters of human adenovirus type 12 and 18. Proc Nat Acad Sc 48:2051-2058, 1962

4. Numazaki Y, Shigeta S, Kumasaka T, et al: Acute hemorrhagic cystitis in children—Isolation of adenovirus type 11. N Engl J Med 278:700-704, 1968

5. Hilleman MR, Werner JR: Recovery of new agent from patients with acute respiratory illness. Proc Soc Exp Biol Med 85: 183-188, 1954

6. Jordan WS Jr, Badger GF, Curtiss C, et al: A study of illness in a group of Cleveland families—X. The occurrence of adenovirus infections. Am J Hyg 64:336-348, 1956

7. Lang WR, Howden CW, Laws J, et al: Bronchopneumonia with serious sequelae in children with evidence of adenovirus type 21 infection. Br Med J 1:73-79, 1969

8. Simila S, Ylikorkala O, Wasz-Hockert O: Type 7 adenovirus pneumonia. J Pediat 79:605-611, 1971

9. Becroft DMO: Bronchiolitis obliterans, bronchiectasis and other sequelae of adenovirus type 21 infection in young children. J Clin Path 24:72-82, 1971

10. Parrott RH, Kim HW, Brandt CD, et al: Vaccination against pediatric illness caused by parainfluenza virus, respiratory syncytial virus and certain adenoviruses—Current status and perspective. M Ann District of Columbia 39:612-614, 1970

11. Klenk EG, Gaultney JV, Bass JW: Bacteriologically proved pertussis and adenovirus infection. Am J Dis Child 124:203-207, 1972

12. Bell TM, Steyn JH: Viruses in lymph nodes of children with mesenteric adenitis and intussusception. Br Med J 5306: 700-702, 1962

13. Girardi AJ, Hilleman MR, Swickey RE: Tests in hamsters for oncogenic quality of ordinary viruses including adenovirus type 7. Proc Soc Exp Biol Med 115:1141-1150, 1964

Cigarette Smoking Ten Years Later

It is now just ten years since cigarette smoking was officially designated a health hazard by the federal government. What has been accomplished is worthy of some examination.

To start at the beginning, it has been more than four hundred years since tobacco was discovered in the Americas and the habit of smoking was transferred to France (1556), Portugal (1558), Spain (1559) and England (1565). It has been over a hundred years (1859) since 68 patients in a hospital in Montpelier, France, were found to have cancer of the lips, tongue, tonsils or elsewhere in the mouth. Sixty-six of these smoked short clay pipes and the use of such pipes soon thereafter fell into disrepute. In 1954 the American Cancer Society and the British Medical Research Council in separate studies observed a higher death rate among cigarette smokers than among non-smokers. In 1962 the Royal College of Surgeons found cigarette smoking a serious hazard to health. In 1963 a second American Cancer Society report showed that death rates had increased over the years as the number of cigarette smokers increased. Just ten years ago, in January 1964, a Special Advisory Committee on Smoking and Health to the Surgeon General of the United States concluded that "cigarette smoking is a health hazard of sufficient importance in the United States to warrant remedial action." Subsequently a number of legal actions were taken and the slogan "Warning: The Surgeon General Has Determined That Cigarette Smoking Is Dangerous to Your Health" has been very widely published.

What has been accomplished by an all-out legally backed educational campaign over a period of a decade may now be examined. According to the Federal Trade Commission the per capita consumption for adults 18 and over was 4,345 cigarettes a year in 1963, 4,186 in 1968, and 4,040 in 1971, with indications that it has remained at about this level since. It also appears that the total number of cigarettes produced has remained fairly constant at something over 500 billion a year. Thus the crude statistical results appear to have been something less than dramatic. To be sure, some people have stopped smoking cigarettes, others no doubt have cut down, but many must also have started. The emphasis on less nicotine and less tar is not to be overlooked, and may have important beneficial effects on the death rates, but it is too early yet to know this. No matter how one looks at it, the results of what has been a very major health campaign over a period of a decade have been disappointing.

There is surely food for thought in this. Much less was accomplished than might have been expected. No doubt others more knowledgeable and statistically sophisticated than the writer will comment. But it seems likely that there are both pharmacological and human factors which have yet to be taken into full account. Drug dependency with all its physiological and psychological ramifications can make it difficult indeed for one who is addicted to cigarettes to quit his habit, and it is worth noting that the campaign addressed itself to health and not to drug dependence. And health and even longevity may not be the high priority for many persons that so often they are assumed to be. Indeed, there is considerable evidence to the contrary. People will often risk health and even survival for some purpose, whether good or bad, or for some momentary thrill or satisfaction. Their reasons for doing this may be either rational or irrational. But this fact of human nature thwarts many noble efforts in public health and preventive medicine, and in medical care as well. These are factors which seem particularly to have come into focus as the results of the ten-year effort to curtail cigarette smoking are examined. Perhaps the campaign for the next decade should take them into more account.

—MSMW

Emergency Medicine

TRUNKEY AND COWORKERS elsewhere in this issue call attention to traumatic injury and to the undeniably inadequate resources, coordination and training in this kind of emergency medicine not only in the West but throughout the nation.

It is unfortunate that *emergency medicine* is a term which so far has no generally accepted definition of meaning. In fact it bids fair to join a number of other widely used and poorly defined terms in medical care such as *primary physician, comprehensive care, consumer,* and even *health care* itself. These terms, like beauty, are readily understood and appreciated in the eyes of the beholder, but may be interpreted entirely differently by someone else. Semantic confusion of this sort seems to abound in medical care and it contributes in no small measure to confused thinking and often to wasteful and very costly action or inaction.

The term *emergency medicine* appears to have a spectrum of meanings. They vary all the way from what is involved in an emergency treatment room drop-in type of ambulatory care to the most complex and urgent medical, surgical or psychiatric catastrophes in or out of hospital. Somewhere in between are equally serious emergencies such as sudden cardiac arrest, acute respiratory failure or acute poisonings. The logistical problems of rendering care in medical emergencies in or out of the hospital are part of emergency medicine. And the number of patients involved at one time may be one or many, perhaps even hundreds in a disaster. There is growing interest in emergency medicine and some believe that it should be recognized as a bona fide specialty. The first step is certainly to define the term and the scope of the subject matter.

Trunkey and his associates are to be commended for drawing attention to a most important phase of emergency medicine which has so far received far less attention than it deserves.

—MSMW

ERRATA

Changes in text and in reference notes:

• *Substitute the following three paragraphs for the final three paragraphs in the item* Abortion *which appeared on page 43,* CALIFORNIA MEDICINE, *Vol. 119, No. 6 (December) 1973.*

Realizing that some physicians may disagree with CMA's position on abortion, whether for moral, ethical, medical or psychiatric reasons and acknowledging the wide spectrum of opinion on the subject, CMA believes that, as with any medical procedure, abortion should never be performed "on demand."[3] CMA holds that no physician may be required to violate his own conscience by performing an abortion; that the procedure be governed by accepted ethical standards, sound clinical judgment, according to the merits of each individual case, and informed patient consent.[4] Nor should any member of the health team be required to assist with an abortion, nor should a hospital be required to permit an abortion in violation of moral principles to which it is dedicated.[5] The alternatives offered to members of the medical profession who oppose abortion are to attempt to: "(1) remove the stigma attached to pregnancy, (2) provide emotional support to the patient during pregnancy, (3) help in adoption, and (4) offer advice regarding contraception and sterilization, according to the conscience of the patient and of the physician."[6]

In all abortion cases, CMA urges the physician to provide pre- and post-abortion counseling and supports policy that recommends family planning counseling.[7]

CMA has established a standing committee "to consider the response of the medical profession to the evolving scientific, technological and philosophical trends in our society as they affect human life."[8] This committee has helped to evaluate policy on abortions, and is delving into other issues which concern society and its relationship to the medical profession.

• *Substitute the following references for those that appeared on page 44, at the end of the item* Abortion, *Vol. 119, No. 6 (December) 1973.*

REFERENCES

"HDR" refers to CMA House of Delegates resolution
"CA" refers to CMA Council action

1. HDR 9-70; HDR 8-73; CA 5/1/70
2. HDR 189-73
3. HDR 8-73; HDR 9-70
4. HDR 8-73; HDR 9-70; CA 6/11/71
5. CA 5/4/73
6. HDR 9-73
7. HDR 9-73; CA 7/28/72
8. HDR 6-71

CASE REPORTS

Refer to: Keys TF: Sternal-costal infection with pseudomonas—A complication of drug abuse. West J Med 120:72-73, Jan 1974

Sternal-Costal Infection with Pseudomonas

A Complication of Drug Abuse

THOMAS F. KEYS, MD, *Rochester, Minnesota*

THE ABUSE CREATED by the self-administration of parenteral drugs, most notably narcotics, is associated with serious medical problems.[1,2] Well recognized systemic complications which arise from the injection of infectious agents include bacterial and yeast endocarditis, pulmonary abscesses, viral hepatitis and malaria. Systemic injection of particulate matter may cause pulmonary edema, pulmonary fibrosis, necrotizing angiitis with aneurysms[3] and chronic active liver disease.[4] Local infections that may occur as well include skin abscesses, phlebitis and the dreaded complication of tetanus.

Not so well recognized are pyogenic infections of the bones and joints. However, recent reports indicate that this complication is more common than was formerly appreciated. In 1971 four heroin addicts were reported with hematogenous osteomyelitis.[5] The vertebral column was involved in three patients and the clavicle in the fourth. Since 1967 Fisbach et al[6] have noted a greater prevalence of Gram-negative bacteria over Staphylococcus aureus in causing vertebral osteomyelitis. Five of the 15 patients in their series were intravenous heroin users. Septic arthritis is also being seen with increasing frequency. Involvement has included the knee, sternoclavicular, achromioclavicular and costochondral joints.[7,8] Pseudomonas aeruginosa appears to be the most common etiologic agent in these cases. Within the past year we have seen two patients with sternal-costal infections caused by this microorganism. It is important to recognize the location of this infection since adequate surgical removal of infected tissue may be required for cure.

From the Section of Infectious Diseases, Department of Medicine, Veterans Administration Hospital, Sepulveda, and the University of California, Los Angeles, School of Medicine.

Submitted March 26, 1973.

Reprint requests to: T. F. Keys, MD, Division of Infectious Diseases and Internal Medicine, Mayo Clinic, Rochester, MN 55901.

Reports of Cases

CASE 1. A 23-year-old man who had been an intravenous methedrine user for one year was readmitted to the hospital in July of 1971 with complaint of progressive painful swelling over the left mid-sternal area since "shooting up" a month previously. Two weeks earlier, an injection of steroid (40 mg Depo-Medrol® in 1 percent xylocaine) into the sternal-costal junction of the third rib had failed to relieve his symptoms. On examination, the patient was afebrile and in no acute distress. His weight was 62 kg. A tender raised mass was noted overlying the mid-sternum and spreading beyond the costochondral junction of the third rib. No drainage or induration was evident. The hemoglobin was 13.9 grams per 100 ml of blood and the leukocyte count was 9,400 per cu mm with a normal differential. The erythrocyte sedimentation rate (Westergren) was 14 mm in one hour. An x-ray film of the chest was normal except for a soft tissue swelling overlying the sternum. Additional views of the sternum demonstrated a destructive process in the upper body with sequestered fragments within the area. The patient was taken to surgery and an incision was made over the sternum across the third rib. Necrotic tissue was encountered extending from the pectoralis muscle through the costochondral cartilage into the sternum. The area was thoroughly debrided, irrigated and packed open with drainage tubes. Cultures of bone, cartilage and muscle grew Pseudomonas aeruginosa. Minimal inhibitory concentrations (MIC's) were 50 micrograms of carbenicillin and 0.78 micrograms of gentamicin per milliliter. Sodium carbenicillin was administered

as an irrigation solution into the wound area for four days. Additionally, the patient received intravenous sodium carbenicillin, 4 grams every four hours for two weeks, and intramuscular gentamicin sulfate, 80 mg every eight to twelve hours for six weeks. Serum creatinine values remained in the normal range during and following therapy. The wound healed completely and when the patient was last seen six months later, he was entirely asymptomatic. Follow-up sternal x-ray films demonstrated residual boney defects from the operation but no evidence of osteomyelitis.

CASE 2. A 45-year-old man who was addicted to heroin was transferred to the Veterans Administration Hospital in February 1972 with pain and purulent drainage from a partially healed wound overlying the sternal-costal junction of the left third rib. Three months previously he had noted the sudden onset of a painful swelling over the left mid-anterior chest lateral to the sternum. A month later the area was explored under local anesthesia at another hospital. An apparent abscess was encountered between the third and fourth costal cartilages. Twenty milliliters of milky fluid was withdrawn and a culture of it grew Pseudomonas aeruginosa. The patient received gentamicin sulfate, 120 mg intramuscularly every eight hours, a dosage that had to be modified because of progressive azotemia. After 24 days, therapy was discontinued. The patient remained afebrile; however, purulent material that was culturally positive for Pseudomonas aeruginosa continued to drain from the surgical wound. In addition he complained of tenderness at the third rib in the mid-clavicular line. Laboratory studies showed hemoglobin of 14.4 grams per 100 ml of blood, leukocyte count of 7,500 per cu mm with a normal differential, and erythocyte sedimentation rate of 11 mm in one hour. No abnormality was noted on a sinogram through the wound drain. An x-ray film of the chest was within normal limits. Special views of the sternum showed no abnormality; however, there appeared to be a moderate amount of soft tissue swelling in the region of the costochondral junction and the mid-portion of the third left rib. Under general anesthesia, the region was explored and necrotic cartilage and rib tissue were found. The area was debrided and the wound loosely packed with a gauze dressing. Quantitative cultures of the material grew 10^5 organisms of Pseudomonas aeruginosa per gram of tissue. Histologic sections of bone were consistent with acute osteomyelitis. MIC's to the isolate were, for carbenicillin 100 micrograms per milliliter, for gentamicin 3.12 mg per ml. The patient weighed 60 kg and his baseline serum creatinine was 0.8 mg per 100 ml. He was treated with sodium carbenicillin, 5 grams every four hours for four weeks by intravenous route, and gentamicin sulfate, 60 mg intramuscularly every eight to twelve hours for four weeks. No reduction in serum creatinine or uninary creatinine clearance occurred following therapy. The wound healed and, when last seen in our clinic 12 months later, the patient had no evidence of recurrence.

Discussion

This report of two patients with sternal-costal infection due to Pseudomonas aeruginosa expands the growing list of bone and joint infections following parenteral drug abuse. Although both patients complained of local anterior chest pain and swelling, there was little evidence of systemic infection at the time they were seen. Temperatures and routine laboratory studies were normal except for slight elevations of the erythrocyte sedimentation rate. Routine chest x-ray studies showed no abnormality but special views of the sternum were helpful in determining the source of infection. At thoracotomy the extent of bone, cartilage and muscle involvement was surprising in view of the apparent benign clinical picture. Treatment consisted of wide excision of devitalized tissue and prolonged systemic chemotherapy.

Summary

Sternal-costal infections due to Pseudomonas aeruginosa developed in two patients who were intravenous drug users. Extensive surgical debridement and systemic chemotherapy with carbenicillin and gentamicin brought about a cure in both.

REFERENCES

1. Louria DB, Hensle T, Rose J: The major medical complications of heroin addiction. Ann Int Med 67:1-22, Jul 1967

2. Cherubin, CE: The medical sequelae of narcotic addiction. Ann Int Med 67:23-33, Jul 1967

3. Citron BP, Halpern M, McCarron M, et al: Necrotizing angiitis associated with drug abuse. N Engl J Med 283:1003-1010, Nov 5, 1970

4. Cherubin CE, Rosenthal WS, Stenger RE, et al: Chronic liver disease in asymptomatic narcotic addicts. Ann Int Med 76: 391-396, Mar 1972

5. Holzman RS, Bishko F: Osteomyelitis in heroin addicts. Ann Int Med 75:693-696, Nov 1971

6. Fishbach RS, Dahlgren JG, Rosenblatt JE: Vertebral osteomyelitis due to gram-negative bacteria. Twelfth Interscience Conference Antimicrobial Agents Chemotherapy Sep 1972, p 93

7. Tindel JR, Crowder JG: Septic arthritis due to Pseudomonas aeruginosa. JAMA 218:559-561, Oct 25, 1971

8. Madhavan T. Salahuddin N, Fisher E, et al: Pseudomonas osteomyelitis in young narcotic addicts. Twelfth Interscience Conference Antimicrobial Agents Chemotherapy Sep 1972, p 93

Refer to: Hale MS, Rodman HD, Lipshin J: Congenital contractural arachnodactyly. West J Med 120:74-76, Jan 1974

Congenital Contractural Arachnodactyly

MEREDITH S. HALE, MD
HOWARD D. RODMAN, MD
JACK LIPSHIN, MD
Panorama City, California

In 1971 R. K. Beals and F. Hecht, University of Oregon Medical School, described a syndrome which they named congenital contractural arachnodactyly (CCA). They reported two affected kindreds observed by them, reviewed similar case reports from a number of countries and distilled from these reports 12 kindreds with findings common to CCA.[1] One of these 12 kindreds was reported by Epstein and several collaborators in 1968 as having "hereditary dysplasia of bone with kyphoscoliosis, contractures and abnormally shaped ears."[2] He outlined reasons why this should be considered a separate genetic entity. McKusick recognized this assertion by including Epstein's kindred in the third edition of his catalog "Mendelian Inheritance in Man," item number 14950.

Outstanding CCA features include congenital joint contractures, arachnodactyly-long, thin digits, dolichostenomelia-long, thin limbs, crumpled ear antihelices, flat ear helices, tibial bowing, metatarsus adductus, gracile incurving toes and fingers, and kyphoscoliosis. About half of the children and all adults with CCA had scoliosis. The early development of progressive severe scoliosis is an important clinical feature of CCA and one that demands timely recognition in order that early corrective treatment may be started before disabling deformity occurs.

CCA transmission is as an autosomal dominant trait; the disorder probably originates as a new autosomal dominant mutation. Affected children are frequently, but not invariably, born by breech delivery. Multiple major joint contractures may be present at birth. These vary in severity; those of lesser severity have been noted to improve spontaneously in early childhood. Finger proximal interphalangeal and metacarpophalangeal joint contractures tend to persist but not to a disabling degree. These finger flexion contractures are not an invariable part of CCA syndrome. When present they are highly visible. Even when absent, the fingers generally assume a flexed and ulnar deviated stance. One CCA patient died at two and a half years of age. Death was attributed to suffocation from laryngeal obstruction.[2] The larynx at autopsy had a narrowed inlet, increased sagittal diameter and prominent epiglottic curvature.

Separating CCA patients from those with overlapping features noted in Marfan's syndrome, homocystinuria, arthrogryposis, osteogenesis imperfecta, Achard's syndrome (brachycephalgia, retroagnathia, gracile digits, thin limbs, no contractures or eye defects) and a syndrome reported by Mirhosseini (arachnodactyly, cataracts and mental retardation) is important for several reasons. These include absence of mental retardation and ocular defects in CCA patients. Cardiac abnormalities are infrequent and those described to date are of no major significance. Finger flexion contractures, when present, do not progress and are not disabling. Contractures of major joints such as the knee tend to improve spontaneously during childhood development. This observation should not in any way delay corrective casting, a treatment that, as is noted in the following case report, is effective. Awareness of the probability that severe scoliosis may develop should lead to early recognition and aggressive treatment of this deformity.[1,3,4]

Shortly after the original CCA report was published (1971),[1] one of us (H.D.R.) evaluated an infant girl, then 11 months of age, referred for a crouched walking pattern and some stigmata of Marfan's syndrome. Notably lacking were ocular and cardiac defects. A survey of this infant's musculo-skeletal abnormalities and her external ear appearance suggested that she might fall in the CCA classification. Subsequent clinical observations, x-ray and laboratory studies (both inclusive and exclusive) confirmed the original CCA diagnostic impression.

Report of a Case

The patient was a baby girl born 15 June 1970 —no siblings, product of a normal full-term pregnancy and vaginal delivery, birth weight 8 pounds,

From the Departments of Physiatry (Dr. Hale); Orthopedics (Dr. Rodman); and Pediatrics (Dr. Lipshin); Kaiser Permanente Medical Center, Panorama City.

Submitted February 9, 1973.

Reprint requests to: M. S. Hale, MD, Department of Physiatry Southern California Permanente Medical Group, 13652 Cantara Street, Panorama City, CA 91402.

TABLE 1.—*CCA Features Compared with Conditions Observed in Patient Reported and Certain Related Syndromes*

Features	*Patient*	*CCA*	*Marfan's*	*Achard's*	*Osteogenesis Imperfecta*
Oval head	+	+	dolichocephaly	brachycephaly	—
Slightly deep set eyes	±	reported	—	—	—
Lower teeth small widely spaced	+	+	—	—	—
High arched palate	+	+	—	—	—
Retroagnathia	+	+	prognathia	reported	—
Flat ear helix	+	+	reported	—	—
Crumpled antihelix	+	+	reported	—	—
Knee flexion contracture	+	+ congenital or early development	later childhood with patellar dislocation	—	—
Gracile limbs	+	+	+	+	—
Arachnodactyly	+	+	+	+	—
Tibial bowing (anterior)	+	+	+	—	—
Incurving toes, fingers	+	+	+	—	—
Finger flexion contracture	Flexion stance only	+ (Uusual but not invariable finding)	—	—	—
Metatarsus adductus	+	+	—	—	—
Hypermobile ankle extension	+	+	—	—	—
Thumb adduction stance	+	reported	reported	—	—
Osteoporosis (x-ray)	+ slight	+ slight	—	—	+ (constant)
Scoliosis	+	+ (Developmental, not congenital)	+	+	reported

(+) = characteristic finding (—) = indicates not a characteristic finding

4 ounces, length 21 inches, uneventful perinatal and neonatal period—was noted by her mother to have "rumpled" ears, thin limbs, long thin fingers and toes. At age nine months she crawled freely but walked in a half-crouched position. Orthopedic evaluation at 11 months of age confirmed a slightly crouched stance when walking and standing, tight hamstring muscles, tibial bowing, metatarsus adductus, arachnodactyly, hypoplastic calf muscles and hypermobile ankle and wrist joints. Hip, spine and foot and ankle x-ray studies showed spina-bifida occulta at the fifth lumbar vertebra and confirmed a mild metatarsus adductus foot abnormality.

At age 14 months repeat orthopedic evaluation showed "typical calcaneus gait . . . long fingers and toes . . . mild metatarsus varus . . . 10-15° knee flexion contracture . . . normal hip motion, anterior bowing of both tibia . . . no x-ray abnormality of knee or ankle growth plates." Successful corrective casting for forefoot adduction and knee flexion contracture was started.

The parents were examined. They had no musculo-skeletal, ocular or ear abnormalities. The infant's grandparents and great grandparents as well as other close kin had no peculiarities in habitus insofar as was known by the parents.

Electromyographic examination of the patient's lower extremities was done at age 15 months. No lower motor neuron or myopathic abnormalities were found. Results of urine amino acid chromatography and mucopolysaccharide studies were normal. Blood cell count, routine urinalysis and creatine phosphokinase reports were normal. X-ray films of the hands, wrists and tibia at age 16 months showed a recognizable degree of osteoporosis, anterior bowing of the tibia and digital arachnodactyly. Ophthalmologic evaluation was within normal limits.

Discussion

The pertinent physical, laboratory and x-ray findings at age 34 months are summarized in Table 1. These are compared in the same table with characteristic findings in CCA, Marfan's syndrome, Achard's syndrome and osteogenesis imperfecta.[4] Homocystinuria, a disease recently distinguished from Marfan's syndrome, has some features in common with CCA but notably lacks congenital joint contractures and is easily distinguished by its characteristic urinary abnormality as well as its recessive mode of inheritance.[3] Figure 1 is photographs of the patient showing some of the salient clinical features of CCA. She was 30 months old when this report was first prepared. At that time she had no clinical or radiographically recognizable scoliosis. Four months later she showed a minimal flexible levoscoliosis of the lower dorsal spine. She walked with a normal heel-toe walking gait and could run easily on

Figure 1.—(A) Neonatal photograph—prominent anterior tibial bowing, CCA ear deformity, retroagnathia. (B) Long, thin incurving toes (age 34 months). (C) Long, thin fingers in characteristic flexion stance, slight ulnar deviation; thumb in usual resting adducted position. (D) Dorsal view of hand and fingers showing arachnodactyly. (E) Characteristic CCA ear, showing flattening of helix, crumpled appearance of antihelix with partial obliteration of concha.

toe-tips. Early hypoplastic calf muscle appearance had diminished. Her height remains in the 97+ percentile (a reported CCA feature). Mental development is normal. The retroagnathia so prominent in her neonatal photograph (Figure 1) has disappeared. Slight metatarsus adductus has remained after corrective casting, but corrective shoes are not considered necessary. The precasting striking excessive ankle dorsiflexion (a reported but not constant CCA feature) now reflects only 30 to 35° of passive ankle dorsiflexion. Other CCA features found in this patient are outlined in Table 1.

Summary

A case report has been presented which the authors believe to be that of a child with congenital contractural arachnodactyly—a "new" syndrome named by Beals and Hecht in 1971. Key physical features and differential diagnostic considerations have been concisely outlined in Table 1. The clinical course of CCA when compared with allied syndromes with overlapping characteristics, includes certain favorable characteristics which alone make recognition of this newly described syndrome important. Anticipation of a severe developmental scoliosis is equally important so that early aggressive treatment can be instituted to preclude unnecessary scoliotic deformity.

REFERENCES

1. Beals RK, Hecht F: Congenital Contractural Arachnodactyly. J Bone Jnt Surg 53-A:987-993, 1971

2. Epstein CJ, Graham CB, Hodgkin WE, et al: Hereditary dysplasia of bone with kyphoscoliosis, contractures, and abnormally shaped ears. J Pediatrics 73:379-386, 1968

3. Beals RK: Homocystinuria. J Bone Jnt Surg 51-A:1564-1572, 1969

4. Hecht F, Beals RK: "New" syndrome of congenital contractural arachnodactyly originally described by Marfan in 1896. Pediatrics 49:574-579, 1972

LETTERS *to the Editor*

Some Order from Chaos

To the Editor: I would like to compliment you on your recent, well written editorial entitled, "From 'Crisis' to Chaos to What?" [Calif Med 119:52-53, Nov 1973]. Any physician who has been engaged in the day-by-day care of medical diagnosis and treatment knows that the situation has indeed become more and more chaotic. The ultimate to that would be collapse with the physicians being incapable of handling the main business at hand, trying to get people well, and perhaps opt for complete salaried physicians in our hospitals. Of course this will not solve the problem at all. There is no way of financing and figuring costs of medical diagnosis and treatment without figuring the number of patients to be seen during a fixed period, the number of beds occupied, et cetera. This is how budgets are figured for all governmental hospitals. Waiting lists and control of patients will then become the order of the day. Unfortunately, the public and their elected representatives are completely naive about this.

The medical society could do something to eliminate some of the chaos and some of the excessive cost by forcing such simple things as unified billings and insurance processing, particularly with the use of the computer. This technology is already at hand and I understand there is one large group in the state that has forced such a system through. In other words, the statement with the diagnosis becomes the insurance form and every insurance carrier, be it public or private, uses it. The recent study by Dr. John Knowles shows that administrative costs in medical care have risen twice as fast as any other costs. It is obvious to anyone, whether in private or institutional practice, that private insurance carriers, Blue Cross, CPS, Medi-Cal, CHAMPUS, industrial accident carriers, Crippled Children's Services, have their own particular requirements for their own forms and methods of billing. To me this is an inexcusable waste and has resulted in an inordinate amount of paper and complexity leading to chaos. You don't have to have a graduate degree in economics to see the effect of this and the geometric proliferation of administration on its concomitant high costs in the medical care system.

The insurance companies and the governmental agencies responsible as third party carriers are operating circa 1930. There is no reason for them not to issue something like a credit card to the patients who are covered. Such a system is being used now in the province of Quebec in Canada.

It would seem to me that the California Medical Association ought to ask the California State Legislature to appoint a commission to intensively study and conduct hearings on the chaos and the costs of administering medical care in 1973. Legislators and the public need education on what is really going on. I am certain that if the legislators had known of the enormous complexity, the vagaries, and the projected costs of the PSRO's, they would never have voted for them in the first place. The majority of the public and their elected representatives do not really know how they are the ones who are going to be controlled.

Your editorial pin-points the current state of affairs. If you have any influence at all on the CMA I think that you might encourage practical action now in attempting at least a partial solution to some of the chaos we are now in, by calling for the reform of insurance claim processing.

Thank you for this opportunity in writing and for your editorial.

Eugene E. Bleck, MD
Hillsborough, California

Editorial Note: The problem extends far beyond California.
—MSMW

Poison Hemlock

To the Editor: In the case report [Costanza DJ, Hoversten VW: Accidental ingestion of water hemlock. Calif Med 119:78-82, Aug 1973] Doctors Costanza and Hoversten have attributed the poisoning in their two patients to Cicuta virosa. The photograph accompanying the article is unquestionably that of Conium maculatum, commonly known as Poison Hemlock. The discussion states that the children confused the hemlock with "wild anise" more commonly known as fennel. The growth characteristics of Conium maculatum

and fennel are very similar in that they tend to grow in fields and not particularly in marshy areas. It would be more likely, therefore, that Conium maculatum would be ingested mistakenly than the Cicuta species. Further investigation reveals that Cicuta maculata which was apparently identified as the ingested plant does not even grow in California, its range being limited to the eastern United States, Canada, Missouri and west as far as Texas. The species of Cicuta that grow in California are Cicuta California and Cicuta douglasii and in a small area around Suisun Bay, a third species, Cicuta voanderli. None of these could conceivably be mistaken for Conium maculatum.

It is possible that the text is all correct and that there was merely a substitution of an incorrect photograph, however, my feeling is that the poisoning was mis-diagnosed as water hemlock poisoning when, in fact, it was poisoning by Poison Hemlock, Conium maculatum.

This becomes important in that the toxic components of the Cicuta is a resinoid while the toxic component of Conium is an alkaloid. Circular 530 from California Agricultural Extension Service reviews extensively the identification and control of poisonous hemlocks in California.

THOMAS O. SCHMIDA, MD
Santa Cruz

REFERENCES

1. Kingsbury JM: Poisonous Plants of the United States and Canada. Prentice Hall, 1964, pp 373-383
2. Tucker JM, Fowler ME, Harvey WA, et al: Poisonous hemlocks, their identification and control. California Agricultural Circular No. 530

* * *

The Author Replies

In an attempt to obtain a clear photograph of the plant water hemlock, I asked a friend who is a ranger at Point Reyes National Seashore to photograph the plant for me. This was the photograph that I submitted. Unfortunately, although we discussed water hemlock, he photographed conium maculata, poison hemlock. Not being a botanist I did not recognize this problem at the time. I still have photographs of the original tubers which Dr. Constance helped us identify. These are water hemlock.

[As to the toxicology report] specifically, we asked for identification of water hemlock but a test for conine was serendipitously performed . . . Conine was not present in the gastric contents. We specifically identified the plant as cicuta virosa not cicuta maculata. However, in our discussion on page 81 while attempting to show that the poisonings of cicuta virosa are like that of cicuta maculata and cicuta vagans we parenthesized the latter two. Hence, it may appear that we were equating these three but in reality we were trying to show their similarities.

I have reverified with Dr. Constance, Professor of Botany at University of California-Berkeley, that the plant these boys ate was indeed water hemlock of the cicuta species. He informs me that cicuta virosa is the old world term and this species may now be known locally as cicuta douglasii. He stated that I might quote him as to the truth that water hemlock grows abundantly in California in marshy areas. The National Park Services' botanist at Point Reyes National Seashore also verifies that water hemlock is abundant here and there are several species in this area.

Let your readers be assured that the poisoning in question and the effects described were due to water hemlock or cicuta species toxicity. This plant grows abundantly in California.

As suggested by Dr. Schmida the photograph was in error. The poisoning, however, was not. Specifically we feel that all physicians in this state should be aware of this poisoning and also this plant which grows in abundance in California.

DAVID J. COSTANZA, MD
San Francisco

Acupuncture and the Law

TO THE EDITOR: I have just learned of the efforts of a law firm in San Francisco to contact many of the physicians in this state to enlist their support in a suit against the Board of Medical Examiners and the Attorney General of the State of California, seeking a court decision to allow the use of non-MD acupuncturists. While I do not question the motives of these attorneys or their clients, the cover letter and the "Draft Complaint" which are being circulated raise some questions which I think must be carefully considered by both plaintiffs and defendants, as well as those who are so far uncommitted or uninvolved. The answers to these questions have major implications for the practice of medicine and the utilization of acupuncture in the United States.

The essence of the argument appears to be that acupuncture, as a new and unfamiliar arrival on

the scene, is foreign to Western medicine and should be regarded as a separate part of "Traditional Chinese Medicine." This separation has produced little but confusion and stalemate in Nevada where a separate Board of Chinese Medicine has been established by the legislature.

The fact of the matter is that acupuncture has been very much a part of American medicine for over a hundred years. The first written report advocating acupuncture in the American literature appeared in the Southern Medical and Surgical Journal in August, 1836, and this was followed later by a report of acupuncture in the Journal of the American Medical Association on October 16, 1897. Sir William Osler was also quite familiar with acupuncture, and it is worth recalling the comments from his classic text, *The Principles and Practice of Medicine:* "For lumbago acupuncture is, in acute cases, the most efficient treatment. Needles of from three to four inches in length (ordinary bonnet-needles, sterilized, will do) are thrust into the lumbar muscles at the seat of pain, and withdrawn after five or ten minutes. In many instances the relief is immediate, and I can corroborate fully the statements of Ringer, who taught me this practice, as to its extraordinary and prompt efficacy in many instances."

Even if one attempts to argue that acupuncture has been neglected and by default is no longer a part of "modern" Western medicine, the increasing interest of the American medical profession and the widespread activity of research centers (from the National Institutes of Health to the medical school campus) refute this argument. The complaint further states: "The practice of acupuncture is so unrelated to modern medicine that medical school training and other related study, and the practice of modern medicine, has furnished no experience, competence or expertise at all for the practice of acupuncture." This is not true since interested medical students, interns and residents, and physicians in practice are increasingly able to obtain experience, competence and adequate expertise in the practice of acupuncture, well within the scope of modern medicine. It would be a tragic mistake to have the courts of this state mistakenly view acupuncture as separate and distinct from the principles and practice of medicine in the traditional and legal sense.

The attorneys also refer to the "normal, natural right as physicians to employ, refer, associate or use other technically trained people" (i.e., the right to use the non-licensed acupuncturist). Although I am a strong supporter of paramedical personnel and their utilization in medical practice. I am reluctant to rush needles into their hands with too much haste, and I am even more reluctant to have a whole new category of paramedical personnel whose only skill is acupuncture and whose only long-term contribution to health care is totally limited to principles and practices from the past. We must indeed learn from the past, but we must also be prepared to adapt and integrate the past into current practice and future planning.

GERALD L. LOONEY, MD
Chairman, Acupuncture Study Group
University of Southern California
School of Medicine, Los Angeles

"Backlash"—A Correction

TO THE EDITOR: I wonder if you would be so kind as to publish this letter to rectify an inadvertent error in my recent article entitled "Backlash" appearing in *California Medicine* 119:76-83, Oct 1973.

In that article I stated that the number of applicants for positions in medical school this year was 70,000. The figure that was intended, was 40,000.

Actually, the last year for which I currently have hard data was the entering class in the fall of 1972 when there were 37,000 applicants for 13,570 first-year enrollments. It is my understanding that the figure has risen a good deal since then but I do not have solid evidence that it ever went as high as 70,000 and a more conservative figure would be 40,000.

In any event, the main point remains unchanged, namely, that despite all the criticisms leveled at American medicine, it is still very attractive to young people.

FRANCIS D. MOORE, MD
Boston

Special Article

Refer to: Pennington M: A review of mandatory continuing medical education in Oregon. West J Med 120:80-87, Jan 1974

A Review of Mandatory Continuing Medical Education in Oregon

MERLE PENNINGTON, MD, *Tualatin, Oregon*

NEARLY SIX YEARS have passed since the Oregon Medical Association agreed that its members should be subject to compliance with minimum standards of performance in continuing medical education. As a result of this decision, some members have been expelled, or have resigned rather than comply with requirements for membership. Today, the association's educational requirement is considered no more than what it really is—merely one of several standards for membership in this state medical association.

In view of the predictions made by many observers when the Oregon Medical Association actually implemented the mandatory education requirement in 1969, it is worthy of note that the association still exists and is in fact a growing and vital organization. Detractors within and outside the OMA's membership prognosticated, at best, mass resignations; and at worst, wholesale refusal to comply with the requirement. Since such eventualities would have rendered the program ineffective and the organization helpless, many delegates who voted for the plan in April, 1968, did so with grave reservations.

The plan, or rather the basic idea from which it sprang, came from the Oregon Medical Association's Council on Medical Education. The council, itself only two years old, had been struggling since its birth with ways and means to improve medical education, particularly for the practicing physician. The Council on Medical Education was created in 1965 by the association's House of Delegates, which felt the state and county medical societies were playing a diminishing role in selecting, producing, and monitoring the scope and quality of continuing education for practicing physicians in Oregon.

The council's charge was to reverse this trend, and in so doing to affect conditions in the state so that education for Oregon's practicing physician was relevant to his needs, practical when applied to the problems he faced, and effective. As demonstration of the high priority attached to these tasks by the House of Delegates, the new panel was given the elevated status of a council as distinguished from a committee. The House of Delegates also raised OMA dues by $10 a year to give the Council on Medical Education adequate funds and the financial independence felt necessary to deal effectively with the problems presented to it.

The council's first two years of existence were devoted to strengthening ties with the University of Oregon Medical School, specialty societies and other purveyors of continuing education for physicians in the state. The council also grappled with a myriad of tangential issues before it finally began to move toward a more direct and active role.

In early 1968, after generating masses of reports, studies and surveys, the council decided it must supplement its detached position as a coordinator and overseer of educational activities

---

Dr. Pennington is chairman of the Oregon Medical Association's Council on Medical Education, a position he has held since 1969. He is also current secretary-treasurer of the Oregon Medical Association.

Reprint requests to: M. Pennington, MD, Chairman, Council on Medical Education, Oregon Medical Association, 2164 SW Park Place, Portland, OR 97205.

for physicians with a more aggressive posture in assuring the quality and effectiveness of continuing medical education in Oregon. Council members were, however, opposed to actually producing programs, feeling that such efforts would be duplicative and extremely expensive.

Establishing Standards

The council decided the OMA could be most effective in influencing the continuing education component of quality medical care by establishing standards for participation in programs, courses, and other less formal educational activities for its own members. It was also decided that some form of quality standards should be applied to medical educational activities in the state. Thus, the decision to make participation in a certain amount of continuing education each year a requisite to association membership came about.

At its midyear meeting in April, 1968, the OMA House of Delegates adopted two recommendations of the Council on Medical Education:

1. That minimum requirements be established for continuing education of the physician members of the Association:
2. That an evaluation mechanism be established regarding the quality of continuing education programs and modalities available.

The House also directed the Council on Medical Education to implement the new policy.

During the ensuing year, the council developed a program which concentrated almost entirely on the first recommendation. At the outset it was agreed that no blanket requirements could be fairly or effectively applied to all members of the association. First, special consideration must be given to members who actually did not practice medicine. In response to this problem the council defined the practice of medicine as, " . . . diagnosis and/or treatment of patients." The council also agreed that life members (OMA members for 30 years who were 65 years of age or older) would not be required to comply by reason of their honored and somewhat honorary status in the association. Resident, intern, and other members in fulltime training would also be exempted from participation.

The council also agreed to recommend that members in ill health, temporary absence from practice, or subject to other extenuating circumstances might be, at least temporarily, exempted from participation in the program. A plan to provide tailor-made requirements for members with special problems was also developed. For example, a physician with a hearing defect might apply to the council for requirements with provisions which did not compromise his ability to fulfill those requirements.

At first the council decided that all other members should adhere to generalized requirements of performance in continuing education each year. However, after some study of this decision, it became clear that no single protocol could be applied to all physicians. The council's change of heart was largely based on results of a study of Oregon physicians' participation in continuing education in its many forms. Responses from various specialties showed wide variance in the modalities considered to be of optimum value. Surgeons, for example, generally ranked formal lectures in their field to be of greater value than any other educational activity, while internists attached less value to didactic presentations than to several others forms of educational endeavor. Respondents' records of time spent in various forms of activity tended to confirm their subjective assessments of the relative value of these activities.

Specialty Requirements

Consequently, a decision was made to develop requirements by specialty, allowing activities to be included or even weighted if they were considered to be of particular value. The council felt such requirements obviously should be developed by the specialties themselves so that such requirements might most clearly reflect the value of various educational activities as assessed by peers in each specialty. Therefore, the various state or regional specialty societies were asked to establish educational requirements unique to their discipline.

In assigning this task to the specialty groups, the council gave two basic criteria which must be incorporated in the requirements in order to be acceptable to the association: (1) Compliance with requirements must involve a certain minimum of participation in terms of time expended (at least 50 hours a year); and (2) compliance with requirements must involve what the group felt was necessary to maintain or improve on the level of knowledge needed to function satisfactorily in the specialty field.

A total of 15 specialty requirements had been developed by April of 1969. Members for whom

specialty requirements had not been established would be asked to fulfill "general requirements" set forth by the council. The general requirements also were and have been used as a model or point of departure in the development of other specialty requirements.

These requirements, a policy statement regarding who must participate and a detailed plan for administration of the program were presented to the House of Delegates in the spring of 1969 under the title "Postgraduate Education Program of the Oregon Medical Association." The selection of the term *postgraduate* rather than *continuing education* has never been clear; however, suffice it to say this somewhat inaccurate title is considerably less colorful than some of the less formal names it has subsequently collected.

The House of Delegates Action

Even though the concept had previously been approved, the Council on Medical Education was apprehensive regarding the House of Delegates' willingness to implement an admittedly controversial program. Surprisingly the policy statement, specialty requirements, and necessary bylaws amendments were unanimously adopted. The House did make a significant change, one which undoubtedly served to strengthen the entire program. After considerable debate, the House directed the council's suggested statement of policy regarding application of the program be further defined so that any physician member of the association engaged in the treatment of patients would be required to complete the educational requirement. The revised version of the policy statement read: "In general all members actively engaged in the diagnosis and treatment of patients, *to even a limited extent,* must participate [in the program]." This new provision meant that all members, even the semi-retired life member physician, would be required to participate fully in the mandatory program.

It was the House's position that if the program was to be of real effect and bearing, it should be universally and uniformly applied. Although this more strict provision has proved to be the source of a great deal of administrative difficulty and hard feelings on the part of older members, four years of experience with the program reveals that the House of Delegates' edict was a wise one.

Finally the House of Delegates directed that the program become effective January 1, 1970. During the eight months before implementation, the council engaged in a "dry run" in an effort to test the administrative portion of the continuing education requirement. Oregon Medical Association members were asked to participate voluntarily in the program based on their record of educational activities for 1969. The experiment was not mandatory, and the option to participate was extended to all members of the association. Of some 2,200 members, 734 had reported on their educational activities by early 1970. Of these, a total of 698 reported participation sufficient to fulfill their respective specialty requirements. Satisfactory completion of the voluntary requirements was noted by a certificate very similar to that of the American Medical Association for its Physician Recognition Award.

Explaining the Program

Officers and staff spent a great deal of time traveling around the state attempting to explain the mandatory as well as the voluntary program. Although these meetings were not always pleasant, they undoubtedly were of value from a public relations standpoint. Individual members were given an opportunity to verbalize their objections and their suggestions, while OMA representatives could at least try to meet these complaints at the outset.

The voluntary reporting experiment indicated several deficiencies in the reporting procedure and the general administrative plan. Association staff had an opportunity to correct these problems before implementation of the mandatory program in 1970. Further, it gave all physicians an opportunity to become aware of the requirements which they would be expected to fulfill in 1970, whether or not they decided to report voluntarily on their 1969 activities.

In preparation for the initial 1970 mandatory reporting year, the association's staff prepared detailed explanatory material as well as a "physician record-keeping card" and a copy of each physician's respective specialty requirements. These packets were mailed to all physician members who were required to participate in the program during 1970. Then, at least until December 1970, the association could do little of consequence to encourage participation in the program, except to insert further amplification and explanation of the program in OMA and specialty newsletters and other periodicals.

Approximately a month before the end of 1970, members required to participate received another

detailed letter of explanation regarding reporting procedures, the importance of participation in the program and a relatively low-key explanation of what they could expect if they did not report activities sufficient to satisfy their requirements. Included with this explanatory letter was a reporting form customized to each participating member's specialty requirements. The form outlined in detail the provisions of each specific activity eligible for credit and where appropriate also noted the dates, titles and locations of major activities in that category. Participating members were also notified that they should report their activities for 1970 no later than February 28, 1971.

It was at this juncture that the great majority of serious objections to the program generally or to its specific provisions surfaced. By the end of January 1971, the Council on Medical Education had received some 200 letters objecting to certain requirements of the program, requesting exemption from mandatory participation because of extenuating circumstances, or simply damning the concept of mandatory education. In addition, the association staff received dozens of calls each day. Generally, however, these calls requested additional information or assistance in completing the reporting procedure properly.

The General Acceptance

Still, despite numerous predictions to the contrary, at the end of January, 1971, 41 percent of the 2,014 members who were required to comply with the program had done so. In early March a second reminder was sent to members who had not yet reported on their 1970 activities. This reminder predictably elicited a new stream of objections, questions, and requests for exemption. However, by March 24 a total of 1,386 of 1,982 members required to participate had complied satisfactorily with their respective specialty requirements. This figure represented 69.9 percent participation, a percentage of compliance approximating the number of members the program's most vehement critics had predicted the association would lose. By May 15 approximately 82 percent of those required to comply had done so.

At that point the members and the staff of the Council on Medical Education initiated an intense personal campaign to elicit responses from remaining members. This effort involved personal telephone calls or correspondence with all nonreporters. These members were reminded of the mandatory nature of the program and were asked to make any comments and suggestions, or to lodge criticisms they felt appropriate. In most cases the physicians advised their interviewer they had simply neglected to report out of forgetfulness or the press of other business. The telephone and letter-writing campaign naturally offered the council and its staff an opportunity to discuss on a personal basis the objections of individual OMA members. This time-consuming and expensive campaign was unquestionably successful, as many physicians immediately reported after being contacted. In fact all but the most severe critics could be convinced the program had value and was here to stay, for by that time the council and its staff had become quite adept at debating the merits of the mandatory program simply because they had heard all the arguments there were to hear.

By late August, 154 members had not reported in satisfaction of their respective specialty requirements. This list was reviewed by the Council on Medical Education and then transmitted to the OMA's Board of Trustees, with a recommendation that the board assume formal jurisdiction over the remaining individuals. At its September meeting the Board of Trustees reviewed the list and consequently voted to declare such members delinquent and to initiate proceedings leading to expulsion, effective December 31, 1971.

By November 5, the list of noncompliers had shrunk to 88 members. Upon review of this list the board adjourned to meet as the association's Board of Censors. It directed the secretary-treasurer to notify members that proceedings to consider their suspension from membership, effective December 31, 1971, would be held on December 12. The formal correspondence was also quite explicit as to what consequences suspension from membership would have with respect to participation in association insurance programs and other benefits of membership. In accordance with association bylaws, approximately a week before the scheduled hearings, each delinquent member was notified as to the time he would be expected to appear to present evidence in his own behalf. Members in this group were also given an opportunity to submit written comments, to waive the hearing entirely, or simply to agree to report before the end of the year.

During the ensuing week 35 more members chose to report rather than to face suspension by the Board of Censors, and the board finally considered the cases of 53 members. Of these, the board exempted four physicians from participa-

tion; accepted the reports submitted by two others; and granted continued hearings to another ten members in order that they be given additional time to take postgraduate courses which would satisfy their requirements. Thus, a total of 37 members were expelled by the board, expulsion to become effective December 31, 1971.

After the disciplined members were so notified, 28 reported before the end of the year, leaving a total of nine members who were actually suspended from membership. Since two of the physicians who had been given continuances were unable or unwilling to complete and report their requirements in the extra time allowed by the board, a total of 11 were actually expelled from membership in the association by March of 1972. Of the 11 subjected to disciplinary action, four physicians eventually completed their requirements, reported them to the association, reapplied for membership, and were subsequently accepted. The total number of permanent suspensions from membership was seven.

News Media and Public Interest

Both supportive and critical observers of the association's program had been primarily concerned with the potential loss of membership due to the mandatory nature of the requirement. They argued that the presence of compulsion in the program was inconsistent with expectations of the typical member regarding a medical association's role. The record really does not support these concerns, for a total of 20 physicians are no longer members because of the compulsory education program's implementation in 1970.

Two members resigned during 1969 after the program was formally adopted. They advised this was a means of formal protest against its adoption. During 1970 five physicians either resigned or were dropped from membership for non-payment of dues. Each cited the continuing education requirement as his reason for withholding dues. In 1971 eight physicians resigned rather than report their educational activities for 1970. Since that time two additional members who either were dropped, resigned or were suspended have reapplied for membership and are participating in this and other OMA programs. Thus, the net loss in membership because of the institution of the compulsory education requirement was 20, considerably less than one percent of the association's current membership.

Although the membership's initial reaction to and performance under the program was considerably more positive than even the most optimistic observers had expected, the eventual reaction of the public and the lay press must be considered most unusual. Although the OMA felt that its action with respect to certain of its members was significant from an internal standpoint, it was most surprised to find an intense interest on the part of the press and the general public.

Shortly after the end of 1971, when the noncomplying members were actually suspended from membership, a brief account of the action was included in the association's newsletter. Since it was felt the situation was of interest only to the profession, no public comment was made. Apparently the newsletter article was picked up by a local reporter, because the association officers and staff suddenly found headline articles in metropolitan Portland newspapers regarding the suspension of several OMA members for "failure to keep up." Before the day ended, many newspapers throughout the country carried similar accounts.

During the days following the appearance of the article in the lay press, the association received hundreds of calls and letters requesting further details, interviews, and, not unpredictably, the names of the physicians who had been expelled. Although some of the calls were from writers for medical periodicals, a significant number were from lay reporters throughout the country. The bulk of the inquiries, however, came from the general public.

The typical caller wanted to know if his doctor was "okay." The association responded that if the individual's physician was a member of the Oregon Medical Association he was not among those who had been suspended for failure to complete educational membership requirements. The association staff was instructed to advise the caller that it was perfectly legitimate for the individual concerned about the fact his physician was not a member to ask the doctor why. The staff also explained there were a variety of reasons why physicians might not belong to the association, and because of these numerous factors the questioner should not draw any conclusions regarding a physician based on his decision not to belong. Additionally, the response was to be positive with respect to association membership: If a physician was a member, he was satisfying certain educational standards of his state medical association.

Although public interest soon tapered off, it is interesting to observe that numerous members

called the association offices asking for a replacement for the OMA membership certificate which they had earlier "lost."

Adjustments in Requirements

After its trial by fire, the program underwent several changes which were designed to make fulfillment of the reporting and record-keeping requirement less burdensome to the individual physician. The major change was extension of the reporting cycle from one year to three. During the first year of experience with the program, it became quite clear that it is really unfair to apply static performance requirements to physicians each year, since most appeared to engage in heavier educational activity periodically rather than constantly or evenly. The association found many members might do very little in the way of continuing medical education during a given year, but the next year might devote a large amount of effort and resources to their professional education.

Beginning in 1971, members were asked to report their activities every year, and were only required to satisfy the requirement by the third year. Although some minor changes in specialty requirements were made because of this change, the primary provision was simply to treble the total requirement. For example, if an internist had been required to report a total of 100 credits during 1970 he would be asked to report a total of 300 credits for the period 1971-73. The OMA has just completed this second phase and is satisfied that the final deadline for this first three-year certification period will pass uneventfully. With a year to go before all members must comply, nearly 70 percent have done so.

Since the institution of the program, the Oregon Medical Association has also negotiated arrangements with the American Medical Association and the American Academy of Family Physicians so that satisfactory performance in the OMA program automatically qualifies appropriate members for the AMA Physician Recognition Award and Academy members for their three-year membership requirement. Conversely, if an Oregon physician chooses to apply independently and receives the AMA Physician Recognition certificate, he is considered to have fulfilled the OMA's education requirement for that period. The same holds true for Oregon family practitioners who maintain membership in good standing with the American Academy of Family Physicians.

Based on its experience with the program, the Council on Medical Education has become considerably more flexible with respect to granting credit or exemption from participation by individual members in special programs. For example, members who contribute a considerable amount of time to the training of emergency medical technicians are allowed generous credit for this activity, regardless of whether or not their individual specialty requirements allow credit for the instruction of paramedical personnel. Other examples include granting of two or three year exemptions for the individual practitioner who may take an abbreviated fellowship or residency in a particular field of interest. Such special dispensation was recently granted to a general practitioner-surgeon in a small industrial town in central Oregon who felt he needed more training to handle the numerous hand and foot injuries with which logging and sawmill worker patients presented him. He decided to take a one-year residency in hand surgery. For this activity, he was granted a two-year exemption from participation in the program.

Evaluation of Courses

The debate regarding the value or even the legitimacy of the mandatory continuing education program continues unabated. Since this descriptive account of the history, current condition, and future plans for this program is not intended to be in its defense, the writer will not attempt to summarize the current status of its pros and cons. It does seem appropriate, however, to point out some very real and measurable benefits which have accrued because of the existence of this program in Oregon. First, there has been a predictable and very healthy increase in interest in programs which are produced for physicians in the state. Since the educational requirements of the association are designed to allow the individual to fulfill the great majority of his requirements without straying far from home and practice, this is not surprising. However, what is surprising and encouraging is the simple fact that Oregon physicians today are demanding a great deal more from the programs which they attend. Based on continuing dialogue with individual physicians, it is the Council on Medical Education's position that Oregon doctors feel if they must meet certain educational requirements, what they do should be of direct benefit to them and to their practice.

In any instance where participants in a program

are provided with an opportunity to subjectively evaluate any given course or program, one criterion of measurement almost always appears in these evaluations—practicality. Today Oregon physicians consistently evaluate an educational opportunity on how it applies to their own practice and how it will better equip them to deal with the problems they see day to day.

Oregon physicians' preoccupation with relevance and practicality in educational programs is to be considered healthy because it demonstrably has made the traditional purveyors of continuing medical education in this state work to provide programs which are indeed relevant to the audience they intend to serve and practical to the needs of that audience.

It is fair to say that at least tangentially because of the mandatory educational program's existence, the typical Oregon physician is beginning to evaluate himself with a mind to seek educational opportunities which will strengthen his abilities as a physician in his own practice.

The Effect on the Learners and Their Association

These general impressions are supported by a preliminary Council on Medical Education staff study which indicates Oregon Medical Association members participate in considerably more continuing medical educational activities now than they did in 1968. This study also reveals in general that Oregon physicians spend more time participating in seminars and courses on limited subjects, rather than in attending meetings and other activities of a more general nature. This shift of desires and attitudes is clearly reflected in the changes which the Oregon Medical Association's annual scientific meeting has undergone. During the past three years this meeting has evolved from one which depended almost entirely on general and specialty scientific sessions to one with few general plenary sessions and a great number of short courses and roundtable discussions on subjects of limited but fairly common clinical interest. This trend in meeting planning is also being followed by most other specialty and voluntary health associations sponsoring educational programs for physicians in the state.

In summary, the major value of the program at present can be identified as a gradual realization by many Oregon practitioners that continuing medical education could much more accurately be described as continuing medical learning and application. In other words, the individual physician's educational needs must be personally assessed with some reference to his peers and their performance. When faced with performing a certain amount of educational activity, the physician takes a more introspective look at exactly what he can do to strengthen his own professional weaknesses.

In order to support and encourage this attitude, the Oregon Medical Association is attempting to initiate programs and other means of education designed to meet the needs of medical communities or, more specifically, the needs of the individual practitioner. Probably the most successful effort of the association for the individual has been the Doctor to Doctor Community Teaching Project (DDCT). The DDCT concept is simply to provide administrative assistance in getting a physician with a personally-determined need together with a physician in his or a nearby community who is particularly adept in the technique or procedure in question. The preceptee then spends a half-day or more in the instructor's office observing and assisting the preceptor with his patients. For example, a general practitioner might see several patients with an orthopedist in the specialist's own office in order to learn how to conduct an adequate examination of the back.

Other efforts by the Council on Medical Education have been intended to encourage continuing programs of local assessment of community needs. Generally such programs have been initiated through the small community hospital, utilizing chart review, PAS and MAP, and other traditional hospital committee tools to determine problems which the medical staff does not handle particularly well. The council then provides assistance in the design of whatever educational or system change is necessary to improve the community's performance.

It is expected that the positive attitudes of physicians regarding their personal continuing educational activities can be strengthened and supported by the association; and the producers of continuing medical education activities can be similarly encouraged to improve the relevance and practicality of their offerings. The development of methods to effectively evaluate these offerings and their effect on the practices of Oregon physicians is clearly a field in which this association is moving more slowly than is desirable. Since the development of a mandatory continuing education program was only one of the two charges assigned

to the Council on Medical Education by the association in 1968, the council must now turn to the creation of a truly effective plan for program accreditation, for the most relevant and practical educational activity is of no value unless it positively affects the practices of the physicians who participate in the program. Ultimately the effect of an educational program must be the improvement of patient care.

Despite considerable testimony to the contrary, the Oregon Medical Association's Council on Medical Education is unconvinced that effective, economical, and practical means of measuring the quality of medical care on an on-going basis are currently available. Of course such a system is the ultimate solution to the problem of defining and measuring competence in medical practice. Such a solution does not yet exist however.

The answer probably lies in the automated and computerized data collection systems which planners of medical peer review systems envision. This route of attacking the problem will undoubtedly be greatly assisted by the implementation of Professional Standards Review Organizations throughout the country. Regardless of the fears held by many physicians with respect to comprehensive peer review systems, particularly those mandated by a government apparently more concerned with cost control than with quality, few can effectively debate that such systems, used properly, will not measure physicians' competence where it really counts—in their offices and at the bedsides of their patients.

Until that time, however, the profession can only offer partial solutions to the problem of systematically monitoring and improving the quality of patient care. Progressive steps in this field are being taken. An excellent example is the development and refinement of the self-assessment model by many national specialty societies. A similar approach is the rapidly growing number of computer-based patient simulations, which offer the practitioner an approximation of the patient encounter where his performance can be compared with that of other physicians.

Periodic recertification by the American Board of Family Practice and the serious consideration of the same move by several other boards is another partial solution. Likewise, mounting opinion in favor of periodic relicensure can be considered a step toward an answer to the problem.

Based on its experience, the Oregon Medical Association feels its mandatory continuing education program is among the several approaches available to the profession in assessing and improving its individual and collective ability to provide optimal care. Still, this and other efforts are no more than temporary means because they do not directly measure nor do they guarantee improvement of actual performance. In short, the Oregon Medical Association does not consider its program a panacea. Rather the program is to be judged as a small but positive step toward dealing with the profession's major responsibility to its patients—assurance that care delivered is of high quality.

Refer to: Hogness JR: The makings of policy for medicine and health—A report on the Institute of Medicine. West J Med 120:88-91, Jan 1974

Special Article

The Makings of Policy for Medicine and Health

A Report on the Institute of Medicine

JOHN R. HOGNESS, MD, *Washington, D.C.*

THE INSTITUTE OF MEDICINE is completing its third year of operation and has moved well beyond the stage of organizing itself and its pursuits. Fourteen different activities have been undertaken since the assembly of a core staff in the spring of 1972. As I prepare to leave the Institute, an invitation from THE WESTERN JOURNAL OF MEDICINE to describe the program and prospects that have been forged is a welcome opportunity to explain why there *is* an Institute of Medicine.

The Institute was chartered in 1970 by the National Academy of Sciences to enlist distinguished members of medical and other professions in activities that will lead "to the advancement of the health sciences and education and to the improvement of health care," as the preamble to our founding document states. Managed neither by government nor the health professions, the Institute is able to bring the talents of a diversely expert membership to bear on health policy projects in the public interest. From these projects come recommendations and alternatives that can be translated into a form usable by those who must make the decisions.

Membership in the Institute is both an honor and a working assignment. Once appointed, members are committed to devote a significant portion of their time to work on Institute panels and committees engaged in a broad range of health policy studies. There are 209 active and five senior members at present. The Institute's charter calls for an eventual active membership limited to 400.

New members are elected annually by current active members from among candidates chosen for their significant contributions to health and medicine, or to such related fields as the social and behavioral sciences, law, administration, and engineering. At least one-fourth of the members must be drawn from professions other than health and medicine, thereby assuring a variety of viewpoints in their deliberations.

The average age of current active members is 51; 61 percent of them hold MD degrees. Members serve for a term of five years and can be reelected for a second term.

The Institute's Function

The Institute's task is to identify, study, and analyze the important issues of health and medicine in order to contribute to the quality of national discussions of them. In the best application of its talents, the Institute tackles issues or problems that affect more than one health profession or segment of the health care enterprise. More often than we usually realize, matters of health professional education, provision of health services, and conduct of biomedical research are closely related to each other.

The functions and potential of the Institute can best be described, I believe, by looking at one segment of its program—in this instance the activities

---

Dr. Hogness will be relinquishing his position as president of the Institute of Medicine on or about April 1 to assume the office of president of the University of Washington, Seattle. He has held the presidency of the Institute since August 1, 1971.

Reprint requests to: J. R. Hogness, MD, President, Institute of Medicine, National Academy of Sciences, 2101 Constitution Avenue, Washington, D.C. 20418.

on health professional education and manpower policies. I select this segment partly because several significant events have recently occurred in it, but also because no segment is more fundamental to the operation of the entire health system. While focusing on the manpower portion, I should point out that a major share of the Institute's activities has to do with the quality, organization and financing of medical and health care. There are other projects dealing with policy on the support and conduct of biomedical research, the prevention of disease and factors affecting health status, and the ethical and legal aspects of health care.

Interdisciplinary Education

The Institute's venture into the field of health professional education began in 1971 with the development of plans for a national invitational conference to explore the problems and possibilities of educating health science students to function as members of an integrated health care "team." While several professional groups had previously met to discuss this matter among themselves, there had not been an opportunity for members of all the major health professions to convene for a consideration of interdisciplinary education. The Institute could provide that meeting ground.

A conference steering committee, with Edmund D. Pellegrino, MD, then vice-president for the Health Sciences at the State University of New York at Stony Brook as its chairman, issued invitations to leaders in medicine, dentistry, nursing, pharmacy, and the fields of allied health. More than 120 people—fairly equally divided among the specialties—attended the conference, which was held October 2 and 3, 1972. The business was conducted in small discussion groups. Among the questions considered: Why do we need to educate teams for the delivery of health care? Who should be educated to serve on the teams? How should education be structured so as to facilitate teamwork? What are the obstacles to interdisciplinary education? Definitive answers were not expected, and were not essayed by the conference. But it did succeed in eliciting a much needed interprofessional dialogue on education.

The 11-member steering committee, after studying the conference proceedings, concluded that "ambulatory care, oriented either toward individuals seeking health care or toward specific population groups, is the most appropriate area in which to begin to develop health care team models." There was unanimous agreement that all health professionals need a better understanding of how their respective functions interrelate with those of others.

Cost of Education

The Institute's most ambitious undertaking to date has been a $2.3 million study of the costs of education in eight different health professions. The study was contracted to the Institute by the Department of Health, Education, and Welfare under provisions of the 1971 Comprehensive Health Manpower Act. Research was begun in July, 1972; a final report is due in January 1974. The study developed methods for estimating the per capita costs of education in schools of medicine, dentistry, osteopathy, optometry, pharmacy, veterinary medicine, podiatry, and nursing, and will provide data on the costs of instruction and education. In addition, the study analyzes the reasons for variation in costs and will make recommendations as to how the cost data can be used to set capitation rates.

The study has been performed by staff members of the Institute of Medicine assisted by a group of consultants. The entire project has been supervised by a steering committee composed of leading specialists in academic and administrative medicine, economics, nursing, health care financing, and medical science. Julius Richmond, MD, Harvard faculty member and director of the Judge Baker Guidance Center in Boston, is chairman of the ten-member Institute committee.

Three different cost-finding approaches have been used:

- Program cost, which seeks at the outset to identify all resources actually used by a school in its operation, and to allocate an appropriate share of these resources to each of its programs independent of the source of funds or the actual cash outlays.
- Net expenditures, which define education as the gross cash expenditures for educational programs, less an allocated amount of revenue earned from patient care and sponsored research. This method attempts to show the relationship of educational expenditures to source of support.
- The constructed cost, which is an attempt to make a model of appropriate resources for medical and other health science schools based on the best judgments of a group of experts in the fields.

Eighty-five schools were visited to obtain data used in the program cost and net educational ex-

penditure approaches. For the constructed cost approach, two groups of academicians and administrators were assembled to deliberate on the construction of hypothetical medical and dental schools. Two seminars were held for this purpose, one in July and the other in September, 1973. A third seminar was held in November to prepare a model of veterinary education. In each seminar two separate workshops developed curricula and teaching modes in the basic and clinical sicences, and then translated those requirements into numbers of faculty needed, taking into account the diverse activities required both to create a suitable educational environment and to assure the continued competence of the faculty.

It was felt at the outset that the range of educational programs and costs in existing health science schools could be partly a result of historical accident, based on the availability of funds. The constructed cost effort was designed to balance the situation. Preliminary results of the workshop sessions indicated that the faculty sizes and divisions of labor specified by the participants were not too different from the situation that exists in schools of "the real world."

Throughout the cost study, the staff and members of the steering committee have had to address very basic questions. What functions and activities beyond instruction are necessary to provide the environment in which a qualified professional is produced? How much research and patient care are needed? Such considerations obviously have a bearing on policy regarding the financing of medical and other health-related education.

Manpower Functions

One of the bigger health matters in United States public policy has to do with the number and type of manpower needed best to deliver medical care. Concern in the 1960s about a possible physician shortage led to the establishment of programs for the training of entirely new categories of health professionals. Medical specialties spawned a variety of physician assistants to handle the routine duties of care. With each new profession has come a new set of professional standards and prerogatives to be protected. It is not at all clear whether the initiatives taken in manpower production are complementary parts of a whole, or conflicting efforts unrelated to one another.

The Institute is planning a study that would approach the matter of manpower requirements for primary care from the point of view of the product. While there are policy issues concerning manpower in the entire health system, primary care is the segment that has experienced the greatest amount of change in structure. The objective of the study would be to define job functions in primary care, rationalize the division of labor among various categories of health workers, and provide concepts of manpower utilization that can be used to eliminate national requirements of various kinds of health workers, both in quantity and geographic distribution.

A planning group of Institute members and other experts is developing a specific study protocol and methodology. The proposal drawn up by this 11-member panel will be presented to the Institute's Program Committee for evaluation.

Other Highlights

As I mentioned earlier, the Institute program during the past year and a half has included a number of other activities concerned with science policy, health care, and the ethical and legal aspects of medicine. Three of them will illustrate several ways in which the Institute responds to opportunities for detailed consideration of policy matters.

The director of the National Cancer Institute, Frank J. Rauscher, Jr., PH D, asked the National Academy of Sciences in August of 1972 to conduct a review of the five-year plan mandated by the Congress for a "targeted" program of research against cancer. Dr. Philip Handler, the Academy's president, in turn requested the Institute to perform the review. A ten-member review panel was formed with Lewis Thomas, MD, then Dean of Yale University School of Medicine, as chairman. The panel's work was confined to the first two of the plan's three volumes, the third not then being available. The review included an evaluation of the way in which scientific priorities had been determined and the proposed techniques for managing the program.

The panel, in its 26-page report, commended "the comprehensiveness and thoroughness" that went into the construction of the cancer plan. But it disagreed with, or certainly questioned, the apparent assumption "that all shots can be called from a central headquarters; that all, or nearly all, of the really important ideas are already in hand; and, that given the right kind of administration and organization, the hard problems can be solved." The panel advised that attention be paid to the development of means for recognizing the

basic science projects essential to the ultimate success of the cancer program. The report was presented to the National Cancer Institute on December 20, 1972.

In the summer of 1972, the Institute sought and received a contract from the Health Services and Mental Health Administration to underwrite a program dealing with the ethical problems encountered in health care decision-making. F. C. Redlich, MD, now professor of psychiatry at Yale University, was appointed chairman of a committee that was to explore various areas of health and medical care and indicate the issues in need of additional study. The committee, which met for the first time in November 1972, drew up six categories of inquiry and invited scholars across the country to prepare papers analyzing topics within these categories. The papers were presented at a conference on Health Care and Changing Values held under Institute auspices November 27-29, 1973. The aim of the conference and other aspects of the committee's work has been to put some order into consideration of the newer ethical issues arising from medicine's scientific and technological advance.

At a general meeting of the Institute in the spring of 1972, the members were asked for suggestions on matters that might be included in the Institute's program. More than 90 ideas came in. One called for an evaluation of recently-legislated Professional Standards Review Organizations (PSRO). The Program Committee accepted the study proposal and referred the matter to the Institute Council. The activity was approved with the proviso that the entire question of quality standards be examined. A panel under the chairmanship of Robert J. Haggerty, MD, of the University of Rochester, has been active since December 1972 in assessing various means of measuring and monitoring quality. Its policy statement, for release early in 1974, will establish generic principles for any system of assuring quality and consider the implications of those principles for the establishment of PSROs.

The Institute of Medicine was created in response to the need for an impartial and broadly representative body that can speak with authority to the issues affecting national health policy. In the three years following its activation, a solid foundation for its analytical evaluations has been laid. With the continued enthusiasm of its members and dedication of its varied staff, the Institute can become a truly significant force for constructive change in our nation's health system.

Special Article

Refer to: Trunkey DD, Lim RC Jr, Blaisdell FW: Traumatic injury—A health care crisis (Special Article). West J Med 120:92-94, Jan 1974

TRAUMATIC INJURY
A Health Care Crisis

DONALD D. TRUNKEY, MD
ROBERT C. LIM, JR., MD
F. WILLIAM BLAISDELL, MD
San Francisco

"Skewered through and through with office pen, and bound hand and foot with red tape."
David Copperfield, by Charles Dickens, Chapter 43

THE MEDICAL PROFESSION must face the fact that trauma is a major unsolved health problem in this country. Trauma has been called the "neglected epidemic of modern society." In 1971 the National Safety Council reported that 114,000 deaths resulted from trauma. An additional 50 million people were injured, and 500,000 disabled and the financial losses incurred came to more than 21 billion dollars. Every day in this country 310 people die, 137,000 are injured, 32,000 are hospitalized and 1,100 are disabled because of trauma (at a cost of 58 million dollars a day). More people died in one year on our highways than died in Viet Nam in ten years. In California during 1970, the Department of Motor Vehicles reported that there were 4,901 deaths and 241,589 injuries from automobile accidents. Accidental death is the Number One killer of people between the ages of one and thirty-six years, and the third largest cause of death in all age groups.

According to the National Research Council, 70 percent of the deaths from automobile accidents occur in rural areas having a population under 2,500. A California study conducted by Waller showed that the mortality rate for persons involved in motor vehicle accidents was 17 per 100,000 population in urban areas, 46.8 per 100,000 population in rural areas and 85.5 per 100,000 population in mountain counties.

Almost all studies have stressed the poor quality of acident care in the United States today. Van Wagoner studied 606 male soldiers with an average age of 26½ years who were fatally injured in civilian accidents in Texas. All of these victims arrived in the hospital alive and fewer than 25 percent died within two hours of arrival. This means that at least 75 percent of these patients survived long enough for their injuries to be appraised and for treatment to be started. However, Van Wagoner found that in 246 (40.5 percent) cases no treatment or supportive care had been initiated before death.

A similar study conducted by Baker reported that of 33 patients who died in 13 Baltimore hospitals, only 11 received what might be classed as "adequate" treatment. In 21 cases (almost two-thirds of the total) there were unacceptable delays in treatment or errors in diagnosis. In seven cases no operation was performed although there were obvious indications for surgical repair.

Other studies, such as the one conducted by

From the American College of Surgeons Northern California Trauma Committee.
Reprint requests to: F. W. Blaisdell, MD, University of California Service, San Francisco General Hospital, San Francisco, CA 94110.

the Chicago Hospital Council, documented the lack of adequate facilities as the cause of needless death. The Chicago Hospital Council found that 59 percent of the 80 hospitals in Cook County did not have observation rooms, 38 percent did not have defibrillators, 23 percent had no x-ray facilities, 90 percent had no emergency room laboratories, 43 percent had no electrocardiogram equipment and 23 percent lacked facilities for positive pressure ventilation.

Another major concern is about the care of trauma victims before they reach hospitals including that given in ambulances, and the adequacy of communications. A recent survey conducted by the American College of Surgeons Northern California Trauma Committee revealed deficiencies on emergency care in many areas of California. The committee reported that the training of ambulance attendants was inadequate, ambulance services were unsatisfactory and emergency facilities were often non-existent. This problem is not unique to California. The State of Pennsylvania requires barbers to attend barber college for 1,500 hours, 50 hours of which must be in anatomy and physiology. Yet Pennsylvania has no licensing requirements for ambulance personnel.

The deficiencies of ambulances have been well documented by the National Academy of Sciences. Of the 25,000 ambulances used in the United States today, no more than a thousand meet the recommended standards for design and equipment. Less than one-tenth of the total of 25,000 are rescue vehicles. Hearses still make up nearly one-fourth of the total; station wagons make up another fourth, and a tenth of the total are panel trucks or vans. Only one-half of the ambulances now in service can communicate with the dispatcher and only one in 17 with the hospital. It has been estimated by the U.S. Public Health Services Division of Emergency Health Service that each year the lives of 60,000 accident victims could have been saved if adequately equipped ambulances with properly trained personnel had been available.

In rural areas there is a dearth of facilities but in metropolitan areas of California a number of emergency departments have been recently created which are actually not equipped to handle real emergencies. This is in part due to a demand for health service that a "drop-in emergency room" can provide, in part to the fact that emergency rooms are used mainly to obtain patients to fill empty hospital beds and increase the utilization of hospital income-producing services such as x-ray and laboratory.

No one denies hospitals are entitled to emergency rooms, provided the consumers understand the level of care being offered. It is critical to differentiate between those emergency rooms offering comprehensive trauma care and those providing only "drop-in" service.

The problem is just the opposite in rural areas. Case loads are not sufficient to support adequate ambulance services. Emergency facilities and communications may be lacking entirely. Hospitals in these areas may be unable to provide even rudimentary facilities for emergency resuscitation, and the personnel often lack the skills to administer emergency care even if facilities were available.

What Can Be Done?

The problems involved in the delivery of adequate trauma care are of four categories: communication, transportation, education, and the adequacy of emergency hospital facilities.

Communication

The initial key to prompt accident care and the most effective utilization of facilities is communications. This is particularly important in rural areas, where lack of communications may be the fundamental obstacle to obtaining access to emergency care.

The statewide adoption of the 911 emergency number would greatly facilitate communications. Access to emergency care would then be as close as the nearest telephone. Calls would be fed into a regional dispatch center and the nearest, most appropriate type of emergency vehicle would be dispatched. When the ambulance arrived on the scene, emergency medical technicians could determine the nature and extent of injury and through the radio establish communications with the nearest, most appropriate emergency facility. Telemetric monitoring in the ambulance during transportation would enable appropriate supportive care to be initiated early enough to permit the patient to be taken to the most appropriate facilities.

Transportation

Emergency ambulance services in rural areas will undoubtedly require state or federal subsidy. In metropolitan areas proper utilization and con-

centration of resources would ensure financial solvency and provide a high standard of care. Public health, fire or police departments and private companies should be encouraged to develop interlocking, non-competing ambulance systems. Regional resources such as Coast Guard, Highway Patrol and military ambulances and helicopters should be recruited to give backup support during catastrophe and to provide rapid transportation of critically injured patients to comprehensive medical facilities.

Education

Education of personnel involved in emergency transportation and emergency room care is essential. The requirements for training of emergency technicians must be defined. Courses currently available in our state colleges should be expanded to meet the needs of those engaged in rescue and emergency care. Physicians must assist in the development of appropriate standards for training.

Emergency Hospital Facilities

Emergency hospital facilities now available must be categorized so that the level of care available in any one emergency facility is known. This will permit the recognition of areas with marginal coverage so that federal or state support can be developed to subsidize critical areas and assure a more uniform level of emergency care. A nationwide system of emergency room classification such as that developed by the Conference on Emergency Care Services in the *Guidelines for the Categorization of Hospital Emergency Capabilities* promoted by the American Medical Association should be adopted.* This would insure that emergency room standards from state to state would be uniform and compatible.

*Representatives include Committee on Trauma-American College of Surgeons, Committee on Injuries of the American Academy of Orthopaedic Surgeons, Airlie Conference on Emergency Medical Services, Committee on Emergency Care of American College of Physicians and the American Hospital Association. (Copy of Guidelines available from AMA, 535 N. Dearborn St., Chicago, Ill. 60610—Single copy $0.45.)

Regionalization would insure the optimal use of highly specialized facilities, would promote well-developed communications and transportation facilities and would eliminate the wasteful duplication that now exists. A regional approach would identify problems and instigate appropriate research into the cause of accidents and emergencies.

The fundamental problem is how to implement recommendations of this type. It is estimated that at the present time there are 42 different committees and agencies addressing themselves to the problems of emergency medical services in the State of California. This degree of fragmentation makes a concerted attack on the problem difficult. There is no coordinating or advisory committee directly responsible to the governor or the state legislature who could advise on appropriate legislation. Given the needed legislation, a decision must be made as to how to develop and implement a comprehensive plan. The State Office of Comprehensive Health Planning or an agency such as the Bureau of Emergency Service of the California State Department of Public Health could assume this role planning if given proper resources and authority. The State Bureau of Hospital Licensing and Accreditation could enforce emergency room standards and help to develop and implement a statewide plan based on regional resources.

The most promising system for emergency medical care in the United States is in Illinois, where the former governor, Richard Ogilvie, endorsed a statewide comprehensive health plan. It is still not a perfect system and is still evolving but it is working and it permits the appropriate use of regional resources as they become available. Such a plan is badly needed in California and because of our relative riches in manpower and resources there is little excuse for delay. The medical profession must anticipate the needs of our citizens and lead the way in promoting a statewide comprehensive emergency system.

WHEN FLU HITS AND HURTS

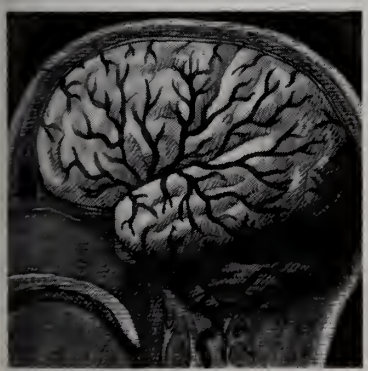
HERE

Muscles and joints

Wherever it hurts, Empirin Compound with Codeine usually provides the symptomatic relief needed.

HERE

Headache



In flu and associated respiratory infection, Empirin Compound with Codeine provides an antitussive bonus in addition to relief of pain and bodily discomfort.

prescribing convenience: up to 5 refills in 6 months, at your discretion (unless restricted by state law); by telephone order in many states.

Empirin Compound with Codeine **No. 3,** codeine phosphate* 32.4 mg. (gr. ½); **No. 4,** codeine phosphate* 64.8 mg. (gr. 1) *Warning—may be habit-forming. Each tablet also contains: aspirin gr. 3½, phenacetin gr. 2½, caffeine gr. ½.

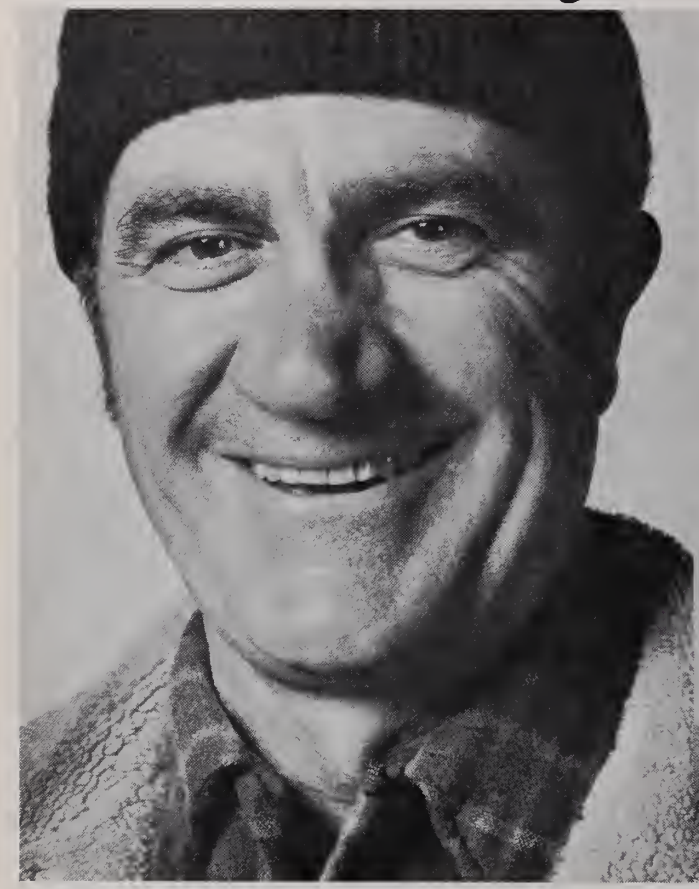
Wellcome

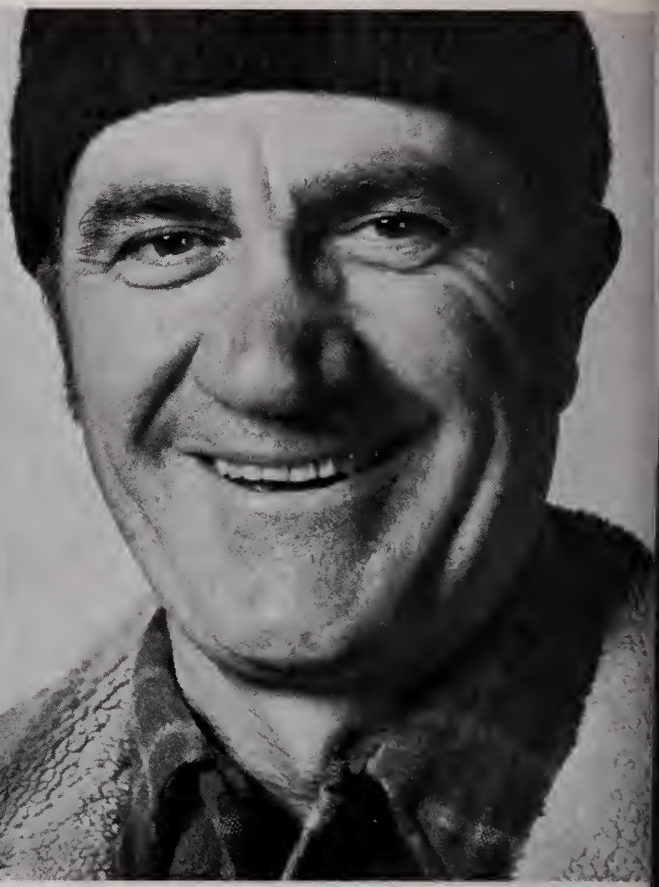
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

EMPIRIN® COMPOUND c̄ CODEINE

#3, codeine phosphate* (32.4 mg.) gr. ½
#4, codeine phosphate* (64.8 mg.) gr. 1

Case history #1





Tom's well-being comes first.

Tom's being well comes first.

Tom, a logging truck driver, lay pinned beneath a runaway log suffering a fractured pelvis, ruptured urethra and severe compound fractures of the left tibia and fibula and was in shock. He was treated at the site, removed to a hospital where he received orthopedic and urologic treatment including multiple surgeries. The injury was reported to State Fund the same day and the first compensation check was sent three days later.

The following day, a representative met with Tom's wife to explain the compensation benefits. Four months following the accident, he was released to return home. His wife worked, so a trained nurse was employed by State Fund to care for him at home. Seven months after the accident, it was determined that Tom needed a bone graft to effect healing of the leg. This was done and a union achieved. Rehabilitation followed, underwritten by State Compensation Insurance Fund and cooperatively supervised by the Department of Vocational Rehabilitation. In time, Tom decided to return to truck driving.

Good medical care, including the help of State Fund, got him on his way to recovery and self-support. Another example of *successful rehabilitation* through the cooperative efforts of State Fund and attending physicians.

Conserving your human resources is our only business

STATE COMPENSATION INSURANCE FUND

Choloxin®

(sodium dextrothyroxine)

Once-a-day dosage.

e reverse side for full prescribing
ormation and dosage schedule.

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015

Choloxin® (sodium dextrothyroxine)

The Lipid-Lowering Agent with Once-A-Day Dosage

Four strengths . . . 1, 2, 4, and 6 mg. . . . are available making the scored tablet regimen a flexible dosage system. And, for most patients, CHOLOXIN tablets offer once-a-day dosage.

AN IMPORTANT NOTE:
It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CHOLOXIN® (sodium dextrothyroxine) Single-Tablet-A-Day Dosage Schedules

See prescribing information in package insert reproduced below.

	Starting Dosage	Increased by Increments of	Usual Maintenance	Maximal Recommended
Adult Hypercholesterolemic	1.0-2.0 mg.	monthly 1.0-2.0 mg.	4.0-8.0 mg.	4.0-8.0 mg.
Pediatric Hypercholesterolemic	0.05 mg./kg. body weight	monthly 0.05 mg./kg.	0.1 mg./kg. body weight	4.0 mg.
Hypothyroid Cardiac Patients	0.5-1.0 mg.	monthly 1.0 mg.	4.0 mg.	4.0 mg.

Choloxin®
(sodium dextrothyroxine)

Description
CHOLOXIN (sodium dextrothyroxine) is the sodium salt of the dextrorotatory isomer of thyroxine. It is chemically described as D-3,5,3′,5′-tetraiodothyronine sodium salt.

Actions
The predominant effect of CHOLOXIN (sodium dextrothyroxine) is the reduction of serum cholesterol levels in hyperlipidemic patients. Beta lipoprotein and triglyceride fractions may also be reduced from previously elevated levels.

Most of the available evidence indicates that CHOLOXIN stimulates the liver to increase catabolism and excretion of cholesterol and its degradation products via the biliary route into the feces. Cholesterol synthesis is not inhibited and abnormal metabolic end-products do not accumulate in the blood.

Indications
This is not an innocuous drug. Strict attention should be paid to the indications and contraindications.

CHOLOXIN (sodium dextrothyroxine) is an antilipidemic agent used as an adjunct to diet and other measures for the reduction of elevated serum cholesterol (low density lipoproteins) in euthyroid patients with no known evidence of organic heart disease.

The drug is also indicated in the treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

Before prescribing, note the following: Results from a randomized clinical study have indicated a possible adverse effect when CHOLOXIN is administered to a patient receiving a digitalis preparation. There may be an additive effect. This additive effect may possibly stimulate the myocardium excessively in patients with significant myocardial impairment. CHOLOXIN dosage should not exceed 4 mg per day when the patient is receiving a digitalis preparation concomitantly. Careful monitoring of the total effect of both drugs is important.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

Contraindications
The administration of CHOLOXIN (sodium dextrothyroxine) to euthyroid patients with one or more of the following conditions is contraindicated:

1. Known organic heart disease, including angina pectoris; history of myocardial infarction; cardiac arrhythmia or tachycardia, either active or in patients with demonstrated propensity for arrhythmias; rheumatic heart disease: history of congestive heart failure; and decompensated or borderline compensated cardiac status.
2. Hypertensive states (other than mild, labile systolic hypertension).
3. Advanced liver or kidney disease.
4. Pregnancy.
5. Nursing mothers.
6. History of iodism.

Warnings
CHOLOXIN (sodium dextrothyroxine) may potentiate the effects of anticoagulants on prothrombin time. Reductions of anticoagulant dosage by as much as 30% have been required in some patients. Consequently, the dosage of anticoagulants should be reduced by one-third upon initiation of CHOLOXIN therapy and the dosage subsequently readjusted on the basis of prothrombin time. The prothrombin time of patients receiving anticoagulant therapy concomitantly with CHOLOXIN therapy should be observed as frequently as necessary, but at least weekly, during the first few weeks of treatment.

In the surgical patient, it is wise to consider withdrawal of the drug two weeks prior to surgery if the use of anticoagulants during surgery is contemplated.

When CHOLOXIN is used as thyroid replacement therapy in hypothyroid patients with concomitant coronary artery disease (especially those with a history of angina pectoris or myocardial infarction) or other cardiac disease, treatment should be initiated with care. Special consideration of the dosage schedule of CHOLOXIN is required. This drug may increase the oxygen requirements of the myocardium, especially at high dosage levels. Treated subjects with coronary artery disease must be seen at frequent intervals. If aggravation of angina or increased myocardial ischemia, cardiac failure, or clinically significant arrhythmia develops during the treatment of hypothyroid patients, the dosage should be reduced or the drug discontinued.

Special consideration must be given to the dosage of other thyroid medications used concomitantly with CHOLOXIN. As with all thyroactive drugs, hypothyroid patients are more sensitive to a given dose of CHOLOXIN than euthyroid patients.

Epinephrine injection in patients with coronary artery disease may precipitate an episode of coronary insufficiency. This condition may be enhanced in patients receiving thyroid analogues. These phenomena should be kept in mind when catecholamine injections are required in sodium dextrothyroxine-treated patients with coronary artery disease.

Since the possibility of precipitating cardiac arrhythmias during surgery may be greater in patients treated with thyroid hormones, it may be wise to discontinue CHOLOXIN in euthyroid patients at least two weeks prior to an elective operation. During emergency surgery in euthyroid patients, and in surgery in hypothyroid patients in whom it may be advisable to withdraw therapy, the patients should be carefully observed.

There are reports that sodium dextrothyroxine in diabetic patients is capable of increasing blood sugar levels with a resultant increase in requirements of insulin or oral hypoglycemic agents. Special attention should be paid to parameters necessary for good control of the diabetic state in dextrothyroxine-treated subjects and to dosage requirements of insulin or other antidiabetic drugs. If sodium dextrothyroxine is later withdrawn from patients who had required an increase of insulin (or oral hypoglycemic agents) dosage during its administration, the dosage of antidiabetic drugs should be reduced and adjusted to maintain good control of the diabetic state.

When either or both impaired liver or kidney function are present, the advantages of CHOLOXIN therapy must be weighed against the possibility of deleterious results.

Usage in Women of Childbearing Age
Women of childbearing age with familial hypercholesterolemia or hyperlipemia should not be deprived of the use of this drug; it can be given to those patients exercising strict birth control procedures. Since pregnancy may occur despite the use of birth control procedures, administration of CHOLOXIN (sodium dextrothyroxine) to women of this age group should be undertaken only after weighing the possible risk to the fetus against the possible benefits to the mother. Teratogenic studies in two animal species have resulted in no abnormalities in the offspring.

Precautions
It is expected that patients on dextrothyroxine therapy will show greatly increased serum protein-bound-iodine levels. These increased serum PBI values are evidence of absorption and transport of the drug, and should NOT be interpreted as evidence of hypermetabolism; similarly, they may not be used for titrating the effective dose of CHOLOXIN (sodium dextrothyroxine). PBI values in the range of 10 to 25 mcg% in treated patients are common.

If signs or symptoms of iodism develop during CHOLOXIN therapy, the drug should be discontinued.

A few children with familial hypercholesterolemia have been treated with CHOLOXIN for periods of one year or longer with no adverse effects on growth. However, it is recommended that the drug be continued in patients in this age group only if a significant serum cholesterol-lowering effect is observed.

Adverse Reactions
The side effects attributed to dextrothyroxine therapy are, for the most part, due to increased metabolism, and may be minimized by following the recommended dosage schedule. Adverse effects are least commonly seen in euthyroid patients with no signs or symptoms of organic heart disease; the incidence of adverse effects is increased in hypothyroid patients, and is highest in those patients with organic heart disease superimposed on the hypothyroid state.

In the absence of known organic heart disease, some cardiac changes may be precipitated during sodium dextrothyroxine therapy. In addition to angina pectoris, arrhythmia consisting of extrasystoles, ectopic beats, or supraventricular tachycardia, ECG evidence of ischemic myocardial changes and increase in heart size have been observed. Myocardial infarctions, both fatal and non-fatal, have occurred, but these are not unexpected in untreated patients in the age groups studied. It is not known whether any of these infarcts were drug related.

Changes in clinical status that may be related to the metabolic action of the drug include the development of insomnia, nervousness, palpitations, tremors, loss of weight, lid lag, sweating, flushing, hyperthermia, hair loss, diuresis, and menstrual irregularities. Gastrointestinal complaints during therapy have included dyspepsia, nausea and vomiting, constipation, diarrhea, and decrease in appetite.

Other side effects reported to be associated with CHOLOXIN (sodium dextrothyroxine) therapy include the development of headache, changes in libido (increase or decrease), hoarseness, tinnitus, dizziness, peripheral edema, malaise, tiredness, visual disturbances, psychic changes, paresthesia, muscle pain, and various bizarre subjective complaints. Skin rashes, including a few which appeared to be due to iodism, and itching have been attributed to dextrothyroxine by some investigators. Gallstones have been discovered in occasional dextrothyroxine-treated patients and cholestatic jaundice has occurred in one patient, although its relationship to CHOLOXIN therapy was not established.

In several instances, the previously existing conditions of the patient appeared to continue or progress during the administration of CHOLOXIN; a worsening of peripheral vascular disease, sensorium, exophthalmos, and retinopathy have been reported.

CHOLOXIN potentiates the effects of anticoagulants, such as warfarin or Dicumarol, on prothrombin time, thus indicating a decrease in the dosage requirements of the anticoagulants. On the other hand, dosage requirements of antidiabetic drugs have been reported to be increased during dextrothyroxine therapy (see WARNINGS section).

Dosage and Administration
For **adult** euthyroid hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN (sodium dextrothyroxine) is 4 to 8 mg per day. The initial daily dose should be 1 to 2 mg to be increased in 1 to 2 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol.

When used as partial or complete substitution therapy for levothyroxine in hypothyroid patients with cardiac disease who cannot tolerate other types of thyroid medication, the initial daily dose should be 1 mg to be increased in 1 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, preferably the lower dosage. The maximum in patients receiving digitalis therapy is 4 mg.

For **pediatric** hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN is approximately 0.1 mg per kilogram. The initial daily dosage should be approximately 0.05 mg per kilogram to be increased in up to 0.05 mg per kilogram increments at monthly intervals. The recommended maximal dose is 4 mg daily, if that dosage is indicated to effect the desired lowering of serum cholesterol.

If new signs or symptoms of cardiac disease develop during the treatment period, the drug should be withdrawn.

How Supplied
CHOLOXIN (sodium dextrothyroxine) is supplied in prescription packages of scored 1, 2, 4, and 6 mg tablets.

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC
Deerfield, Illinois 60015

103rd Annual Session
AND
Western Scientific Assembly

MARCH 2-6, 1974 • HILTON HOTEL • SAN FRANCISCO

PLAN TO ATTEND THE PROGRAMS
and
VISIT THE SCIENTIFIC EXHIBITS

Among the topics:

- ☐ 8th ANNUAL CANCER SYMPOSIUM
  Primary treatment of breast cancer
- ☐ SPECIAL CONFERENCE
  Human sexuality and its medical complications
- ☐ SPECIAL CONFERENCE
  Alcoholism and drug dependence are medical problems—and socio-political issues
- ☐ GENERAL AND FAMILY PRACTICE
  Emergency care—medicine's "untamed frontier"
- ☐ ANESTHESIOLOGY / CHEST DISEASES
  Before, during, and after surgery—pulmonary problems
- ☐ INDUSTRIAL MEDICINE / NEUROLOGY / ORTHOPEDICS / PHYSICAL MEDICINE / PSYCHIATRY
  Rehabilitation and the disabled worker
- ☐ **Allergy, Dermatology, Neonatology, Gynecology, Oncology, Genetics, Pathogenic Viruses, and much, much more**

(For Hotel Reservations see Page 26 of Advertising Section)

APPLICATION FOR HOTEL ACCOMMODATIONS

103rd Annual Session • MARCH 2-6, 1974

CALIFORNIA MEDICAL ASSOCIATION and WESTERN SCIENTIFIC ASSEMBLY

SAN FRANCISCO HILTON HOTEL • SAN FRANCISCO

Registration Opens Friday Afternoon, March 1

SCIENTIFIC SESSIONS
Begin Saturday Morning, March 2

HOUSE OF DELEGATES OPENING SESSION
Saturday Afternoon, March 2

---

1. Fill in the form below **completely** for room accommodations at the CMA's 1974 Annual Session.
2. Your reservation request should include the definite date and hour of your arrival and departure.
3. All reservations, **except for suites,** must be made through the San Francisco Hilton Hotel, Mason at O'Farrell Street, San Francisco, Ca. 94102, **by February 2, 1974.**
4. **All SUITE reservations must be cleared through the CMA Convention Office, San Francisco.** If you are requesting a suite, direct your requests to: CMA Convention Office, 731 Market Street, San Francisco, Ca. 94103.
5. **Cancellations:** Please notify San Francisco Hilton Hotel, Mason at O'Farrell Street, San Francisco, Ca. 94102, of all cancellations.

   Changes: All other changes are also to be made directly with hotel at all times.

SAN FRANCISCO HILTON HOTEL

	Main Building	Tower
Singles	$23-39	$33-48
Twins or doubles	$32-48	$42-57
Additional person in room	$ 9	$ 9
1 Bedroom suites	$74 & up	$95 & up

Send to: SAN FRANCISCO HILTON HOTEL RESERVATIONS
Mason at O'Farrell Street, San Francisco, Ca. 94102

Please reserve the following accommodations for the CMA's 1974 Annual Session in San Francisco, March 2-6, 1974:

Please Check Preference: ☐ MAIN BUILDING ☐ MAIN BUILDING FLOOR 5-11 ☐ TOWER
(INSIDE FREE PARKING AVAILABLE FLOORS 5-11 MAIN BUILDING)

Single Bedroom $_____ Twin-Bedded $_____ Double Bed $_____ Suite $_____

Arrival (date) _____ Hour _____ a.m. p.m. Departure (date) _____ Hour _____ a.m. p.m.

The name and address of each hotel guest must be listed. Include names and addresses of each person in a double or twin-bedded room, and names and addresses of **all other persons** for whom you are requesting reservations.

Your Name _____

Address _____ County _____

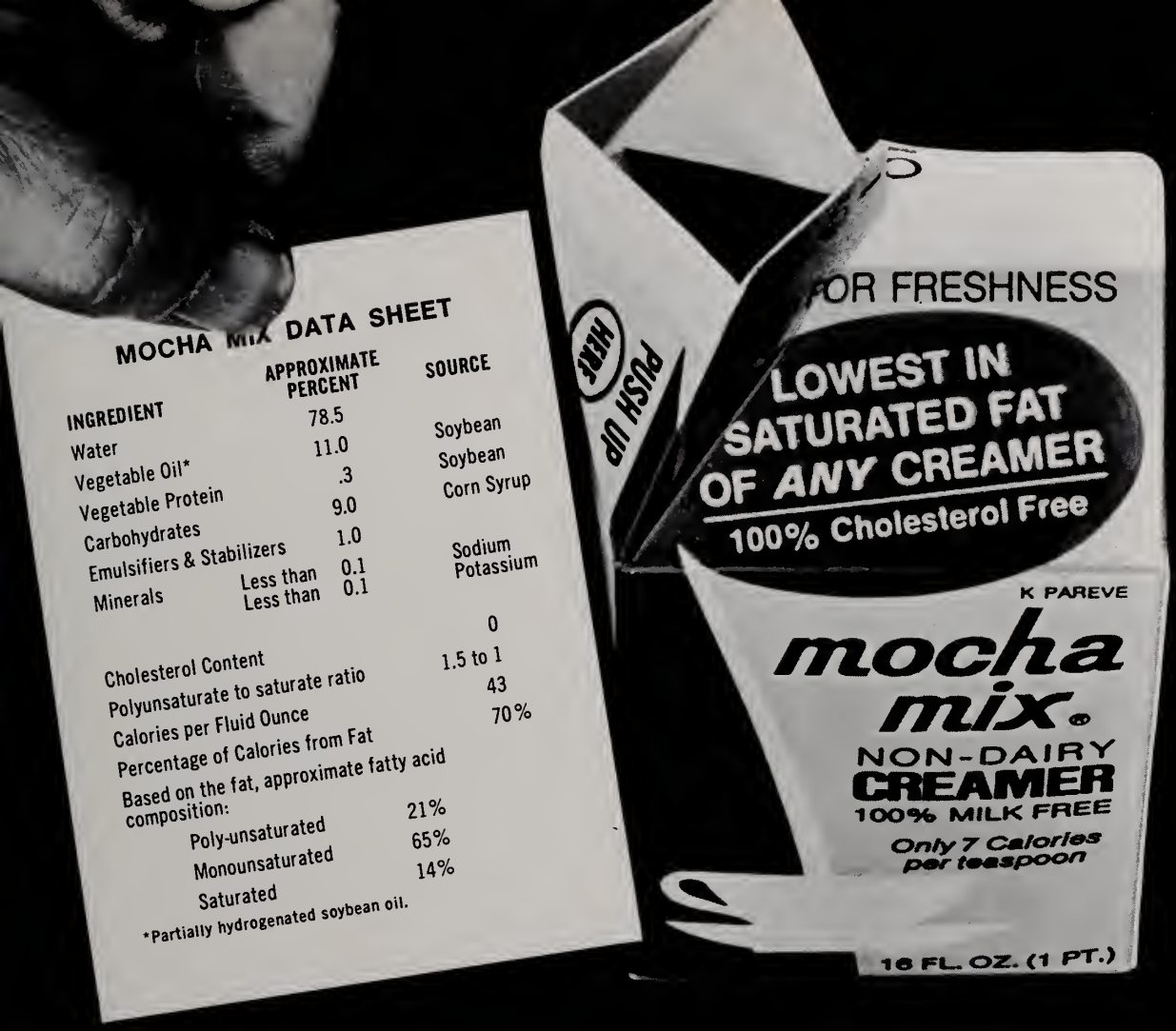
City and State _____ Zip Code _____

GUESTS' NAMES AND ADDRESSES:

_____

_____

_____



Mocha Mix® presents its credentials:

Study them. Note how low Mocha Mix® is in saturated fat. (Actually the lowest of any creamer — liquid, frozen or powdered.) Then note the unsaturated to saturated fat ratio (1.5:1). And Mocha Mix is 100% milk-free and 100% cholesterol-free, too! Taste? In coffee . . . on cereal, fruit or desserts . . . or for cooking, any way, any time a creamer is called for, Mocha Mix is the most delicious creamer ever!

In addition to the 16 oz. size found in the dairy case of most grocery stores, Mocha Mix is available in larger sizes and ½ oz. portion packs for hospitals and institutions.

Interested? Send us a note and we will send you a supply of coupons your patients can redeem at their grocers. Hospital service may also be supplied upon request. Mail to: Mocha Mix Dept. Presto Food Products, Inc. P.O. Box No. 21908, Los Angeles, Calif. 90021

mocha mix. . . . the non-dairy creamer that's lowest in saturated fat!

In Gonorrhea

Injection WYCILLIN®

(sterile procaine penicillin G suspension) Wyeth

Penicillin in large doses remains the drug of choice in therapy of gonorrhea. Among penicillins, first choice recommended by the national Center for Disease Control for parenteral therapy of uncomplicated gonorrhea is aqueous procaine penicillin G.

Administration of 4.8 million units together with 1 gram oral probenecid, preferably given at least 30 minutes prior to injection, is recommended in treatment of uncomplicated gonorrhea.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reaction.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated) — Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, preferably given at least 30 minutes prior to injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units. I.M divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N gonorrhoeae.* Follow-up treatment consists of 4.8 million units daily or 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each TUBEX® disposable syringe 2,400,000 units (4-cc. size) contains procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.7% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. The multiple-dose 10-cc. vial contains per cc. 300,000 units procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, mg. polyvinylpyrrolidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Denise has VD.

Let's keep it from getting around.

Actual new cases of infectious syphilis apparently reached the 100,000 mark during the past year; new cases of gonorrhea, more than 2.5 million. That VD is rampant again is due, in large part, to the multiple contacts of teenagers like Denise.

By administering adequate doses of the recommended types of penicillin, you can usually cure VD in the beginning stages. And destroy another link in the chain of infection.

In Syphilis

Injection

BICILLIN® Long-Acting (sterile benzathine penicillin G suspension) Wyeth

Benzathine penicillin G...a drug of choice recommended by the national Center for Disease Control in all stages of syphilis and in preventive treatment after exposure.

Administration of 2.4 million units (1.2 million in each buttock) of benzathine penicillin G usually • cures most cases of primary, secondary and latent syphilis with negative spinal fluid • helps break chain of infection • minimizes chance of immediate reinfection.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular benzathine penicillin G.—Venereal infections: Syphilis, yaws, bejel and pinta.

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: 2,400,000 units in 4-cc. single dose disposable syringe. Each TUBEX disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. Units benzathine penicillin G (as active ingredient); 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. polyvinylpyrrolidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Wyeth Laboratories • Philadelphia, Pa. 19101

When low back pain* interferes...

Help relieve pain, restore mobility with

PARAFON FORTE® Tablets

PARAFLEX® (chlorzoxazone)† 250 mg.; TYLENOL® (acetaminophen) 300 mg

*This drug has been evaluated as "possibly" effective for this indication.

See brief summary of prescribing information on facing page for Indications, Contraindications, Warnings, Precautions and Adverse Reactions.

© McN 73

PARAFON FORTE® Tablets help relieve pain, restore mobility and stop pain-spasm feedback by providing:

a nonsalicylate analgesic equal to aspirin for relief of pain,[1,2] yet unlikely to cause the gastric irritation,[2,3] allergic reactions[2] or increased bleeding time[4] associated with aspirin therapy.

and a skeletal muscle relaxant shown in extensive clinical studies to be useful in a variety of low back disorders[5-7]* but which is not an antihistamine or tranquilizer derivative and is unlikely to produce a tranquilizing or sedative effect.[8]

*Indications Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective for the relief of severe skeletal muscle pain and spasm when associated with acute disorders of the lower back (including acute exacerbations of chronic conditions).

Contraindications: Sensitivity to either component.
Warnings: *Usage in Pregnancy*—Use in woman of child-bearing potential only when potential benefits outweigh possible risks.
Precautions: Exercise caution in patients with known allergies or history of drug allergies. If a sensitivity reaction or any signs or symptoms suggestive of liver dysfunction are observed, the drug should be stopped
Adverse Reactions: Occasionally, drowsiness, dizziness, lightheadedness, malaise, overstimulation or gastrointestinal disturbances may be noted; rarely, allergic-type skin rashes, petechiae, ecchymoses, angioneurotic edema or anaphylactic reactions. In rare instances, *Paraflex* (chlorzoxazone) may possibly have been associated with gastrointestinal bleeding. While *Paraflex* (chlorzoxazone) and chlorzoxazone-containing products have been suspected as being the cause of hepatic toxicity in approximately eighteen patients, it was not possible to state that the dysfunction was or was not drug induced.
Usual Adult Dosage: Two tablets q.i.d.
Supplied: Scored, light green tablets, imprinted "McNEIL"—bottles of 100.

References: 1. Batterman, R.C., and Grossman, A.J. Fed. Proc. *14*:316, 1955 2. Goodman, L.S., and Gilman, A., ed. The Pharmacological Basis of Therapeutics, ed. 4 New York, The Macmillan Company, 1970 3. Vickers, F.N. Gastroint. Endosc. *14*:94, 1967 4. Mielke, C.H., Jr., and Britten A.F.H. New Engl. J. Med. *282*:1270, 1970 (Corresp.) 5. Vernon, W.G. Curr. Therap. Res. *14*:801, 1972 6. Scheiner, J.J. Curr. Therap. Res. *14*:168, 1972 7. Walker, J.M. Curr. Therap. Res. *15*:248, 1973 8. Friend, D.G. Clin. Pharmacol. Ther. *5*:871, 1964

†U.S. Patent No. 2,895,877

McNEIL McNeil Laboratories, Inc.
Fort Washington, Pa. 19034

BOOKS RECEIVED

Books received by CALIFORNIA MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

CARDIAC PACING—Edited by Philip Samet, MD, Chief, Division of Cardiology, Department of Internal Medicine, Mount Sinai Medical Center, Miami Beach, Professor of Medicine, University of Miami School of Medicine, Coral Gables, Florida. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 427 pages, $21.00.

DERMATOLOGY—2nd Edition—Patrick Hall-Smith, MD (Edin), FRCP (Edin & Lond), Consultant Dermatologist, Brighton and Lewes and Mid-Sussex Groups of Hospitals; Robert J. Cairns, MD, BS (Lond), FRCP (Lond), Consultant Dermatologist, Central-Kent, Medway and Gravesend, Tunbridge Wells and Leybourne Groups of Hospitals; and F. L. B. Beare, MB, BS (Lond), FRCS (Eng), Consultant Plastic Surgeon, St. Mary's Hospital, London, Queen Victoria Hospital, East Grinstead, and Brighton General Hospital. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973, 374 pages, $18.50.

DR. THOMPSON'S NEW WAY FOR YOU TO CURE YOUR ACHING BACK—Jess Stearn. Doubleday & Company, Inc., 277 Park Avenue, New York City (10017), 1973. 203 pages, $7.95.

DuVRIES' SURGERY OF THE FOOT—Third Edition—Editor: Verne T. Inman, MD, PhD, Professor of Orthopaedic Surgery and Director, Biomechanics Laboratory, University of California, San Francisco. Foreword by J. B. deC. M. Saunders, MD, LL D, D SC, FRCS(E), Regents Professor, University of California, San Francisco. The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, MO (63141), 1973. 567 pages, $27.50.

FAMILY CARE—A Guide—Edited by Naomi Baumslag, MD, Associate Professor of Preventive Medicine and Community Health, Emory University, Atlanta. The Williams & Wilkins Company, 428 East Preston St., Baltimore (21202), 1973. 392 pages, $7.95.

THE FIRST FIVE YEARS—A Relaxed Approach to Child Care—Virginia E. Pomeranz, MD, Pediatrics Department, New York Hospital, and Assistant Clinical Professor of Pediatrics, Cornell University Medical College; and Dodi Schultz. Doubleday & Company, Inc., 277 Park Avenue, New York City (10017, 1973. 248 pages, $6.95.

FLEXIBLE IMPLANT RESECTION ARTHROPLASTY IN THE HAND AND EXTREMITIES—Alfred B. Swanson, MD, Chief, Orthopaedic Surgery and Orthopaedic Research, Blodgett Memorial Hospital, Chief, Orthopaedic Surgery, Kent Community Hospital, Chief, Orthopaedic Training Program, Blodgett Memorial Hospital and Butterworth Hospital, Chief of Staff, Mary Free Bed Hospital and Rehabilitation Complex, Consultant, Michigan Area Juvenile Amputee Clinic, Grand Rapids, Clinical Professor of Surgery, Michigan State University. The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis (63141), 1973. 352 pages, $37.50.

INTERACTIONAL PSYCHOTHERAPY—Stages and Strategies in Behavioral Change—Sheldon Cashdan, PhD, University of Massachusetts, Amherst. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 150 pages, $7.50.

MALE AND FEMALE HOMOSEXUALITY—A Comprehensive Investigation—Marcel T. Saghir, MD, Assistant Professor of Clinical Psychiatry, Washington University School of Medicine, St. Louis, Missouri; and Eli Robins, MD, Wallace Renard Professor and Head of the Department of Psychiatry, Washington University School of Medicine. The Williams & Wilkins Company, 428 East Preston St., Baltimore (21202), 1973. 341 pages, $11.95.

PHYSICIAN'S HANDBOOK—Seventeenth Edition—Marcus A. Krupp, MD, Clinical Professor of Medicine, Stanford University School of Medicine, Director of Research, Palo Alto Medical Research Foundation; Norman J. Sweet, MD, Associate Professor of Medicine, University of California, San Francisco; Ernest Jawetz, PhD, MD, Professor and Chairman, Department of Microbiology, Professor of Medicine, Lecturer in Pediatrics, University of California, San Francisco; Edward G. Biglieri, MD, Associate Professor of Medicine, University of California, San Francisco; and Robert L. Roe, MD, Assistant Professor of Medicine, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1973. 727 pages, $6.50.

RURAL AND APPALACHIAN HEALTH—Edited by Robert L. Nolan, MD, MPH, JD, Professor and Chairman, Division of Public Health and Preventive Medicine, Professor of Pediatrics, West Virginia University School of Medicine; and Jerome L. Schwartz, MBA, DrPH, Visiting Professor of Public Health and Preventive Medicine, West Virginia University School of Medicine and Professor of Community Health, University of California, Davis, School of Medicine. Charles C Thomas, Publisher, 301-327 East Lawrence Ave., Springfield, IL (62703), 1973. 249 pages, $11.50.

A SURGEON'S ODYSSEY—Loyal Davis, MD. Doubleday & Company, Inc., 277 Park Avenue, New York City (10017), 1973. 336 pages, $8.95.

TECHNIQUES OF FAMILY PSYCHOTHERAPY—A Primer—Edited by Donald A. Bloch, MD, Director, Nathan W. Ackerman Family Institute, New York. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 124 pages, $7.50.

(Continued on Page 32)

(Continued from Page 31)

WHO'S LISTENING?—Leonard E. Read. The Foundation for Economic Education Inc., 30 South Broadway, Irvington-on-Hudson, NY (10533), 1973. 208 pages, $2.50 (paperback), $4.00 (cloth).

AGENTS OF BACTERIAL DISEASE—Albert S. Klainer, MD, Professor of Medicine, Chairman, Division of Infectious Diseases, West Virginia University School of Medicine, Morgantown; and Irving Geis, New York City. Medical Department, Harper & Row, Publishers, Inc., 2350 Virginia Avenue, Hagerstown, MD (21740), 1973. 188 pages, $9.95.

ALIMENTARY TRACT ROENTGENOLOGY—Second Edition—Volumes 1 and 2—Edited by Alexander R. Margulis, MD, Professor and Chairman, Department of Radiology, University of California, San Francisco; and H. Joachim Burhenne, MD, Clinical Professor of Radiology, University of California, San Francisco, Chairman, Department of Radiology, Children's Hospital and Adult Medical Center, San Francisco. The C. V. Mosby Company, Publishers, 11830 Westline Industrial Drive, St. Louis (63141), 1973. 1690 pages total, in volumes 1 and 2; $100.00.

BUILDING A GROUP PRACTICE—Fred W. Wasserman, MPH, MBA; and Michael C. Miller, MPH, Instructors, University Extension Programs, University of California, Los Angeles. Charles C Thomas, Publisher, 301-327 East Lawrence Avenue, Springfield, IL (62717), 1973. 178 pages, $7.95, Cloth; $5.50, Paperback.

CLINICAL GYNECOLOGIC ENDOCRINOLOGY AND INFERTILITY—Leon Speroff, MD, Robert H. Glass, MD, and Nathan G. Kase, MD, Department of Obstetrics and Gynecology, Yale University School of Medicine. The Williams & Wilkins Co., 428 East Preston Street, Baltimore (21202), 1973. 266 pages, no price given.

CLINICAL NEUROSURGERY—Volume 20—Proceedings of the Congress of Neurological Surgeons, Denver, Colorado, 1972—Editor-in-Chief: Robert H. Wilkins, MD. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1973. 500 pages, $22.50.

CURRENT PSYCHIATRIC THERAPIES—Volume 13—Edited by Jules H. Masserman, MD, Professor Emeritus of Psychiatry and Neurology, Northwestern University, Chicago. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 238 pages, $15.00.

CURRENT SURGICAL DIAGNOSIS AND TREATMENT—Edited by J. Englebert Dunphy, MD, Professor of Surgery and Chairman, Department of Surgery, University of California, San Francisco; and Lawrence W. Way, MD, Associate Professor of Surgery, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1973. 1108 pages, $14.00.

THE DIABETIC FOOT—Edited by Marvin E. Levin, MD, Assistant Professor of Clinical Medicine, Washington University School of Medicine, Associate Attending Physician, Jewish Hospital, St. Louis; and Lawrence W. O'Neal, MD, Associate Professor of Clinical Surgery, Washington School of Medicine. The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, MO (63141), 1973. 262 pages, with 249 illustrations, $25.50.

GASTROINTESTINAL DISEASE—Pathophysiology-Diagnosis-Management—Marvin H. Sleisenger, MD, Professor and Vice Chairman, Department of Medicine, University of California, San Francisco, Chief, Medical Services, Veterans Hospital, San Francisco; and John S. Fordtran, MD, Professor of Medicine, The University of Texas Southwestern Medical School at Dallas, Senior Attending Physician, Parkland Memorial Hospitals, Dallas, Editors. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1973. 1659 pages, $37.50.

HANDBOOK OF OCULAR THERAPEUTICS AND PHARMACOLOGY—Fourth Edition—Philip P. Ellis, MD, Professor and Head, Division of Ophthalmology, Department of Surgery, University of Colorado Medical Center, Denver; and Donn L. Smith, MD, PhD, Director of the Medical Center, Dean of the College of Medicine, University of South Florida College of Medicine, Tampa. The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, MO (63141), 1973. 262 pages, $14.75.

HYPERPARATHYROIDISM—Edward Paloyan, MD, Associate Chief of Staff for Research and Education, Veterans Administration Edward Hines, Jr., Hospital, Hines, Illinois; Professor of Surgery, Loyola University, Stritch School of Medicine, Maywood, Illinois; Ann M. Lawrence, MD, Associate Professor of Medicine, The University of Chicago Pritzker School of Medicine, Chicago; and Francis H. Straus, MD, Associate Professor of Pathology, The University of Chicago Pritzker School of Medicine, Chicago. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 222 pages, $16.00.

HYPERTENSION: MECHANISMS AND MANAGEMENT—The Twenty-Sixth Hahnemann Symposium—Edited by Gaddo Onesti, MD, Professor of Medicine, Kwan Eun Kim, MD, Associate Professor of Medicine; and John H. Moyer, MD, Professor of Medicine, Hahnemann Medical College and Hospital, Philadelphia. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 902 pages, $39.00.

MARIJUANA: MEDICAL PAPERS 1839-1972—Edited by Tod H. Mikuriya, MD. Medi-Comp Press, 2633 East Twenty-Seventh Street, Oakland, CA (94601), 1973. 465 pages, $22.00 (available only from Medi-Comp Press).

MENSENDIECK—Your Posture and Your Pains—Ellen B. Lagerwerff and Karen A. Perlroth. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1973. 240 pages, $7.95.

PROLOID® (thyroglobulin)
Caution: Federal law prohibits dispensing without prescription.

Description. Proloid (thyroglobulin) is obtained from a purified extract of frozen hog thyroid. It contains the known calorigenically active components, Sodium Levothyroxine (T_4) and Sodium Liothyronine (T_3). Proloid (thyroglobulin) conforms to the primary USP specifications for desiccated thyroid—for iodine based on chemical assay—and is also biologically assayed and standardized in animals.

Chromatographic analysis to standardize the Sodium Levothyroxine and Sodium Liothyronine content of Proloid (thyroglobulin) is routinely employed.

The ratio of T_4 and T_3 in Proloid (thyroglobulin is approximately 2.5 to 1.

Proloid (thyroglobulin) is stable when stored at usual room temperature.

Indications. Proloid (thyroglobulin) is thyroid replacement therapy for conditions of inadequate endogenous thyroid production: e.g., cretinism and myxedema. Replacement therapy will be effective only in manifestations of hypothyroidism.

In simple (nontoxic) goiter, Proloid (thyroglobulin) may be tried therapeutically, in nonemergency situations, in an attempt to reduce the size of such goiters.

Contraindication. Thyroid preparations are contraindicated in the presence of uncorrected adrenal insufficiency.

Warnings. Thyroglobulin should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 0.5 to 1.0 grain (32 to 64 mg) and increased by the same amount in increments at two-week intervals. This demands careful clinical judgment.

Morphologic hypogonadism and nephroses should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.

Myxedematous patients are very sensitive to thyroid and dosage should be started at a very low level and increased gradually.

Precaution. As with all thyroid preparations this drug will alter results of thyroid function tests.

Adverse Reactions. Overdosage or too rapid increase in dosage may result in signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.

Dosage and Administration. Optimal dosage is usually determined by the patient's clinical response. Confirmatory tests include BMR, T_3 ^{131}I resin sponge uptake, T_3 ^{131}I red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Clinical experience has shown that a normal PBI (3.5-8 mcg/100 ml) will be obtained in patients made clinically euthyroid when the content of T_4 and T_3 is adequate. Dosage should be started in small amounts and increased gradually with increments at intervals of one to two weeks. Usual maintenance dose is 0.5 to 3.0 grains (32 to 190 mg) daily.

Overdosage Symptoms. Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

(Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)

How Supplied. ¼ grain; ½ grain; scored 1 grain; 1½ grain; scored 2 grain; 3 grain; and scored 5 grain tablets, in bottles of 100 and 1000.

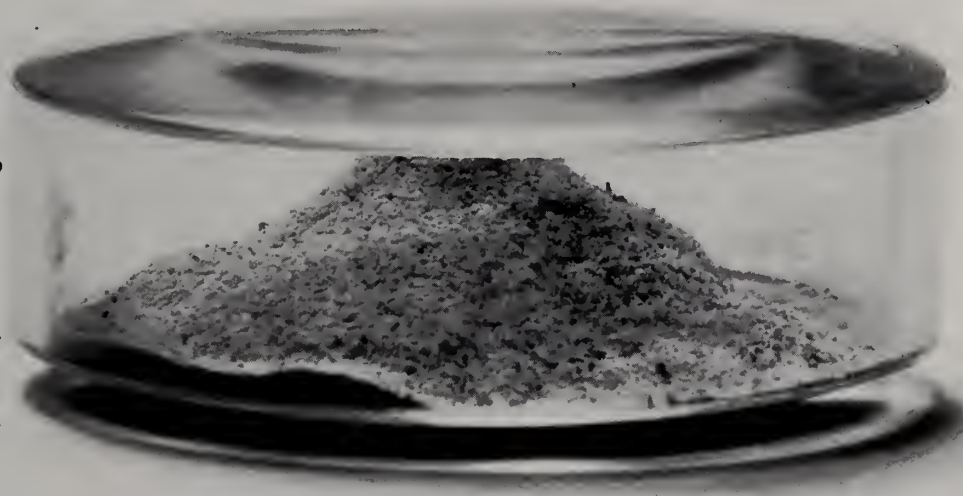
Full information available on request.

WARNER/CHILCOTT
Division, Warner-Lambert Company
Morris Plains, New Jersey 07950

PR-GP-31-B/W

IN NATURAL THYROID THERAPY:

ARE PATIENTS GETTING THE POTENCY YOU PRESCRIBE?



Unlike U.S.P. desiccated thyroid, Proloid®(thyroglobulin) offers the assurance of constant potency.

To begin with, Proloid is uniquely purified. The thyroglobulin extracted from hog thyroid is devoid of any glandular debris.

Then, Proloid is chemically and biologically assayed to assure consistent metabolic activity from batch to batch. The T_4 and T_3 content of every dose is blended for optimal thyroid replacement.

Important, too, is the fact that Proloid is invariably "fresh" when your patients take it. Under proper storage conditions, its potency will not diminish for at least four years.

All of which adds up to this: the potency of Proloid is constant...for more consistent results.

PROLOID®
(thyroglobulin)

natural thyroid therapy that leaves nothing to chance

Classified Advertisements

The rate for each insertion is **$2.50 per line** (average six words per line) **with five line minimum.**

Box number charge: $1.50 each month.

Classified display rates $25.00 per inch.

Copy for classified advertisements should be received not later than **the fifth of the month preceding issue.** • Classified advertisers using Box Numbers forbid the disclosure of their identity. Your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the rules of the Advertising Committee.

CLASSIFIED ADVERTISEMENTS ARE PAYABLE IN ADVANCE

PHYSICIANS WANTED

INTERNIST, GENERALIST AND UROLOGIST, State Veterans Home and Hospital. Salary depending upon training, experience and position to be filled. Excellent retirement plan and other benefits. Located one hour from San Francisco in beautiful Napa Valley. Call or write John P. Preston, Administrator, Phone (707) 944-2422.

LOS ANGELES-ORANGE COUNTIES. Growing HMO needs more General Practitioners, Pediatricians, Orthopods, OB/GYN's and ENT. Competitive salaries, regular increases and tax-sheltered fringe benefits. Two newly opened medical centers. Send your curriculum vitae to: Frank Eaton, MD, Medical Director, Family Health Program, Room 1419, 2925 Palo Verde, Long Beach, CA 90815.

ORTHOPEDIST: Board certified or board eligible, for large multispecialty group, to replace retiring orthopedist. Department consists of 7 orthopedists and 2 physician assistants. Department and area expanding. The Permanente Clinic, 5055 North Greeley Ave., Portland Ore. 97217

GPs: Golf, swim, water ski, snowmobile, fish, ski, minutes away. New 56-bed hospital opening November 1973. Adjacent clinic with room for 8 MDs under construction. Join group of 3 young MDs or solo. Contact Leland Reichelt, MD, Davis Clinic, Wadena, Minnesota 56482. Call collect (218) 631-1360 or Earl Schillo, Administrator, Wesley Hospital, Wadena, Minn. 56482. Collect (218) 631-3510.

SITUATIONS WANTED

NEPHROLOGIST-INTERNIST—Calif. Lic. University trained, board eligible Internal medicine, 2 years nephrology fellowship (1 yr laboratory, 1 yr clinical incl. ARF, CRF, dialysis, transplantation) seeks position preferably in Central or Northern California. Write The Western Journal of Medicine, 731 Market St., Box 9370, San Francisco, CA 94103.

PRACTICES FOR SALE

SAN DIEGO—High Volume Medical Practice 450M+ including x-ray and laboratory—excellent potential for expansion. Seeks HMO buyer. Terms of sale—Take over leaseback payments—equipment and sale of accounts receivable—Seller wants active interest in New Organization. Write The Western Journal of Medicine, 731 Market St., Box 9368, San Francisco, CA 94103. Replies held confidential.

SOUTHERN CALIFORNIA, ORANGE COUNTY; Solo Ped Practice available near University Teaching Hospital. Active and growing. Over 100,000 gross last year. Good coverage for Night and Vacations. Cash or terms available. Write The Western Journal of Medicine, 731 Market St., Box 9369, San Francisco CA 94103.

OFFICES FOR LEASE OR RENT

ATT. FAMILY PHYSICIANS—Very attractive medical office available on Balboa Peninsula. Bldg. consisting of joint reception room with Dentist. Consult. rm., Exam. rm., ENT. Recovery rm., Lab. Private parking. Referral patients from former Dr.—Call 673-0169 or 673-9140.

HEMET—For Rent—2 medical suites in new medical center adjacent to community hospital. 10th fastest growing area in U.S.—Smog Free—Lease with First 2 months Free. Phone (714) 658-3261.

NEW MEDICAL SUITES AVAILABLE in an Orange County Bldg with established doctors and diagnostic screening center. Desirable location with off street parking, carpets, drapes, air conditioning. Leasing office on premises. Grove Professional Bldg. No. 108, 9355 Chapman Ave., Garden Grove, CA 92641. Ph. (714) 539-1811.

REAL ESTATE FOR SALE

DOCTOR'S IDYLLWILD MT. RETREAT—First time offered. Cabin with cedar and redwood outside, like new. 2 BR, 1½ Bath, Privacy, View and Sun. 27,500.00. Owner will carry. Phone (714) 328-4827.

LOCUM TENENS WANTED

DOC-TOUR—Need **Locum Tenens** physicians for ships, theater tours, and rock group tours. Physicians Extended Care Medical Group, Inc., 2550 Webster St., San Francisco, CA 94115; (415) 921-2550.

EDUCATIONAL PROGRAM

PHYSICIAN EDUCATION PROGRAM in Family Planning at UCLA. Sponsored by the American College of Obstetrics and Gynecology. Approved for credit by the American Academy of General Practice. A one week, no tuition, seminar, March 11-15, 1974, covering the areas of Clinical Contraception, Family Planning Administration, and Human Sexuality. After attending the seminar physicians have the option of returning for 2-4 days of clinical skill development (no tuition) and/or learning surgical procedures (tuition). For more information contact Irvin M. Cushner, MD, OB-GYN Department, UCLA, Center for the Health Sciences, Room 24-139, Los Angeles CA 90024. Telephone (213) 825-1046.

WITHOUT YOUR HELP, WE COULDN'T HELP

Nationwide, Retail Credit Company completes almost half a million Attending Physicians' Statements and Underwriting Medical History Reports each year, providing a vital service to the insurance industry at the least possible inconvenience to you.

Thanks to the cooperation of thousands of doctors across the continent, we help to assure the rapid flow of insurance underwriting and claim information. Anytime you have a question about the services we perform, don't hesitate to call us:

RETAIL CREDIT COMPANY

Home Office: Atlanta, Ga.

Information for Business Decisions

San Francisco 752-0530
Los Angeles 385-0171
Portland, Ore. 288-5721
Seattle 284-4063

TEXTBOOKS FOR SALE

MANUAL OF ROUTINE ORDERS FOR MEDICAL AND SURGICAL EMERGENCIES

published by

WARREN GREEN, Inc.

10 South Brentwood Boulevard

St. Louis, Missouri 63105

CASETTE/SPEECH INSTRUCTIONS

MAKE YOUR TECHNICAL KNOWLEDGE EFFICACIOUS when you speak. New concise 60 minute cassette gives basic speech instructions for the busy professional people. SATIS. GUAR. Don't delay send $7.00 check or money order now to, CURTIS, P.O. Box 4597 M, Sacramento, CA 95825. CALIF TAX 5%.

COMPTON FOUNDATION HOSPITAL

820 West Compton Boulevard

COMPTON, CALIFORNIA 90220

(213) 537-3070

(213) 631-1148

G. CRESWELL BURNS, M.D.
Administrator and Medical Director

HELEN RISLOW BURNS, M.D.
Assistant Medical Director

MEMBER OF

American Hospital Association

and

National Association of Private Psychiatric Hospitals

High Standards of Psychiatric Treatment . . . Serving the Los Angeles Area

Accredited by Joint Commission on Accreditation of Hospitals

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine,** Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

ALCOHOLISM AND DRUG USE

February 8-9—**Dealing with Drugs.** UC Extension, Riverside. Friday-Saturday. Contact: UC Extension, Riverside 92502. (714) 787-4105.

CANCER

January 16—**Malignant Lymphoma.** Hospital of Good Samaritan and American Cancer Society at Hospital of Good Samaritan, Los Angeles. Wednesday. 6½ hrs. $35. Contact: Janie Sternal, Cont. Med. Ed., Hosp. of Good Samaritan, 1212 Shatto St., Los Angeles 90017. (213) 482-8111, ext. 224.

January 18-19—**Symposium—American Cancer Society, Kern County Unit.** Casa Royale Motor Inn, Bakersfield. Friday-Saturday. 11 hrs. Contact: Donald C-S Tan, MD, 2807 "H" St., Bakersfield 93301. (805) 324-0211.

February 23—**Newer Developments in Gynecologic Cancer.** UCD. Saturday.

February 27-March 3—**Conference on Oncology—2nd Annual.** UCLA at Riviera Hotel, Palm Springs. Wednesday-Sunday.

March 14-15—**Urology Symposium—Cancer of the Genito-Urinary Tract.** See Surgery, March 14-15.

March 21-22—**Clinical Cancer Conference—9th Annual.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday.

Continuously—**Tumor Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. Tuesdays, 4:00 p.m. Contact: Sidney Saltzstein, MD, University Hospital, San Diego. (714) 291-3330, ext. 1071.

Continuously — **Tumor Board — Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Pathology Conference Room, Harbor General Hospital, Torrance. Fridays 3-4 p.m. Advice and consultation from specialists in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: John Benfield, MD, Dept. of Surgery, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 281.

MEDICINE

January 16—**Pediatric Dermatology.** USC at Womens Hospital, Los Angeles. Wednesday.

January 23—**Pediatric Dermatology.** USC at Womens Hospital, Los Angeles. Wednesday.

January 24-25—**Medicine '74.** See Of Interest to All, January 24-25.

January 26—**Severe Respiratory Failure.** PMC. Saturday.

January 26—**Current Concepts in Nutrition Dietary Management in Renal Disease.** USC. Saturday.

February 2—**Practical Pointers in Chest Disease.** UCD. Saturday.

February 13—**Diabetes.** USC. Wednesday.

February 13—**Clinic on Thyroid Disease.** UCSF at Community Hospital, Santa Cruz. Wednesday.

February 15-17—**Theory and Practice in Echocardiography.** UCLA. Friday-Sunday.

February 20-22—**Current Concepts in the Diagnosis of Pulmonary Disease.** California Thoracic Society at Hyatt on Union Square, San Francisco. Wednesday-Friday. 24 hrs. $125 for members; $150 for non-members. Contact: Elma Plappert, Exec. Secy., CTS, 424 Pendleton Way, Oakland 94621. (415) 636-1756.

(Continued on Page 38)

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Arthur Selzer, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.

UCD: University of California, Davis
Contact: George H. Lowery, MD, Professor and Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-3170.

UCI: University of California, California College of Medicine, Irvine
Contact: Donald W. Shafer, MD, Assistant Coordinator, Continuing Medical Education, Regional Medical Programs, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

At Your Service in The Golden State

In the region named *California* by Spanish adventurers probably after the name of a treasure island in a popular Spanish tale . . .

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY, MISSOURI 64137

is represented by . . .

Dick Bastin

Vito Bell

Mel Bergman

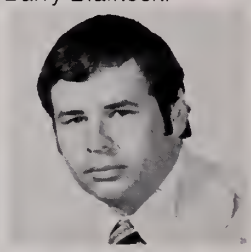
Barry Bialkoski

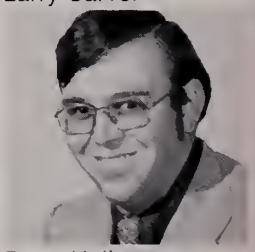
Larry Carver

Dave Evans

Bob Fatch

Richard Foss

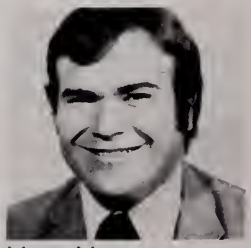

Dave Hawks

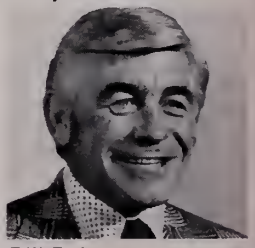

Barry Heilman

Bob Jones

Randy Kennick

Ruth MacKie

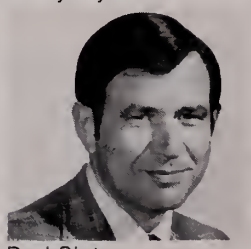

Marty Myers


Bill Palmer

John Patella

Jim Petric

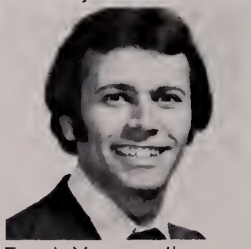
Mike Ryan


Bud Sinkey

Ernie Smith

Bill Stauch

Lorin Waxman


Frank Yannarell

These representatives bring you . . . . . .

Puts comfort in your prescription for nicotinic acid

THE OPTIMAL DOSE, 400-mg, timed-release NICO-400® (nicotinic acid) capsule provides

- Controlled flushing for the desired effects without therapy-limiting side effects.
- Convenient b.i.d. dosage that's less likely to be forgotten.
- The economy of nicotinic acid medication.

For comfort wherever nicotinic acid is used

NICO-400®

(nicotinic acid) Plateau CAPS®

MARION

(Continued from Page 35)

February 22—**Myasthenia Gravis.** USC at International Hotel, Palm Springs, Friday.

February 22-23—**Program for Diabetes.** UCD. Friday-Saturday.

February 22-23—**American College of Physicians—20th Southern California Regional Meeting.** Town and Country Hotel, San Diego. Friday-Saturday. 16 hrs. $20 for members; $25 for non-members. Contact: D. R. Tourtellotte, MD, Gen. Chr., 6896 Magnolia Ave., Riverside 92506.

March 1-2—**American College of Physicians—Northern California and Nevada Region.** St. Francis Hotel, San Francisco. Friday-Saturday. $20. Contact: Maurice Fox, MD, Governor, 300 Homer Ave., Palo Alto. (415) 321-4121.

March 4-8—**Arrhythmias Retreat.** USC at Erawan Gardens, Indian Wells. Monday-Friday.

March 12—**Dermatology.** USC at Womens Hospital, Los Angeles. Tuesday.

March 13—**Fluid and Electrolyte Workshop.** UCSF at Community Hospital, Santa Cruz. Wednesday.

March 19-22—**Consultants' Course in Dermatology.** UCSF. 27 hrs. $150. Tuesday-Friday.

March 20-May 22—**Hematology.** UCLA. 2 months; Wednesdays.

March 25-April 5—**Intensive Review of Internal Medicine.** USC. 2 weeks.

Continuously—**Clinical Conferences.** Community Hospital of Santa Cruz. See Of Interest to All, Continuously.

Continuously—**Medical Chest Conference.** St. Mary's Hospital, San Francisco. Tuesdays, 4:00-5:00 p.m. in Pulmonary Classroom. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Medical Morbidity-Mortality Conference.** St. Mary's Hospital, San Francisco. Thursdays, 12:15-1:00 p.m. in Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Clinical Cardiology Conferences.** San Diego County Heart Association at University Hospital, San Diego. Thursdays, 8-10 p.m. Contact: Robert O'Rourke, MD, Instructor, Univ. Hospital, San Diego. (714) 291-3330, ext. 1644. Or Mrs. Cathy Ware, Prog. Dir., San Diego Co. Heart Assn., 3640 5th St., San Diego 92103. (714) 291-7454.

Continuously — **Differential Diagnosis in Internal Medicine.** USC. Fourth Thursday of each month, 7:30-10:00 p.m. September 27, 1973-May 30, 1974.

Continuously—**Renal Dialysis Traineeships.** UCSF. By special arrangement.

Continuously—**Preceptorships in Biochemistry and Biophysics.** UCSF. By arrangement.

Continuously—**Clinics in Dermatology.** UCSF. By arrangement.

Continuously—**Cardiovascular Seminars.** Mondays at 4:30 p.m. in the second floor lecture hall, Basic Science Building, UCSD. Contact: UCSD.

Continuously—**Preceptorships in Cardiology.** American College of Cardiology and PMC. By arrangement. Contact: Arthur Selzer,, MD, PMC; or Miss Mary Anne McInerny, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

Continuously—**Biomedical Lecture Series.** UCSD. Specified Wednesday at 8:00 p.m. For schedule contact UCSD.

Continuously—**Joint Continuing Medical Education Programs for South Bay Hospitals.** UCSD, Bay General Hospital, Chula Vista Community Hospital, Coronado Hospital, Paradise Valley Hospital and CRMP. Programs to be held at various hospitals. Contact: UCSD.

Continuously—**Neurology Conference.** San Joaquin General Hospital, Stockton. Mondays, 10:00-11:30 a.m. in Conference Room 2. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Renal Conference.** San Joaquin General Hospital, Stockton. First Thursday of each month, 11:00 a.m. to 12:00 noon, Conference Room 2. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Wednesday of each month, 10:00-11:30 a.m., Conference Room 1. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Seminar in Clinical and Public Health Aspects of Chest Diseases.** Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Three-hour sessions on second Friday of each month, 9-12 a.m., B-3 classroom, Chest Wards. Presentation of patients demonstrating medical, social, and public health aspects of chest disease, followed by discussion of cases. Course open to physicians, nurses, social workers and personnel concerned with detection and management of patients with chest disease. No fee. Contact: Matthew Locks, MD, Dir., Chest Ward Service, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1245.

Continuously—**Training of Physicians in Modern Concepts of Pulmonary Care.** CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George C. Burton, MD, LLU.

Continuously—**Neurological Sciences.** St. Francis Hospital of Lynwood. Wednesdays, 7:30-8:30 a.m. Presentations of radiological evaluations and pathological specimens of current material and review of current topics in specialty. Weekly notification of cases available. Contact: Ralph Miller, Admin. Asst., St. Francis Hospital of Lynwood, 3620 Imperial Hwy., Lynwood 90262. (213) 639-5111, ext. 365.

Continuously—**Continuing Education in Internal Medicine—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12:00-1:00 p.m. Systematic review of internal medicine, lectures by faculty and visiting professors. Contact: A. James Lewis, MD, Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 647.

Continuously—**Training for Physicians in General Internal Medicine.** CRMP Area VI and LLU at LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

Continuously—**EKG Conference.** St. Francis Hospital of Lynwood, Lynwood. Presented the first Thursday of each month, 12:00-1:30 p.m. A presentation of cases and pathology of recent coronary patients. Contact: Ralph Miller, Admin. Asst., St. Francis Hospital of Lynwood, 3630 Imperial Hwy., Lynwood 90262. (213) 639-5111, ext. 365.

Continuously — **Cardio-angiography Conference.** St. Francis Hospital of Lynwood, Lynwood. Presented the second and fourth Thursday of each month, 12:00-1:30 p.m. Contact: Ralph Miller, Admin. Asst., St. Francis Hospital of Lynwood, 3630 Imperial Hwy., Lynwood 90262. (213) 639-5111, ext. 365.

Continuously—**Basic Home Course in Electrocardiography.** One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. $125 (52 issues). Contact: USC.

Continuously—**Cardiology Conferences — CRMP Area III.** Monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations

of local complicated cardiological problems. Contact: William J. Fowkes, Jr., MD, 703 Welch Road, Suite G1, Palo Alto 94304. (415) 321-1200, ext. 6015.

Grand Rounds—Medicine

Tuesdays

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

9:00-10:00 a.m., Morrissey Hall, St. Mary's Hospital, San Francisco.

Neurologist in Chief Rounds. 12:30 p.m., 6 East, University Hospital of San Diego County, San Diego. UCSD.

Wednesdays

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

1st Wednesday of each month, 10:00-11:15 a.m., Conference Room 1, San Joaquin General Hospital, Stockton.

10:30-12 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., University Hospital, UCSD.

12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

Thursdays

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

10:30-12:00 noon, Room 63-105, UCLA Medical Center. UCLA. Second, Third, and Fourth Thursdays.

Neurology. 11:00 a.m., 664 Science, UCSF.

Neurology. 12:30 p.m., University Hospital of San Diego County, San Diego. UCSD.

4th Thursday of each month, 12:30 p.m. in lower conference room, Huntington Intercommunity Hospital, Huntington Beach.

Fridays

8:00 a.m., Auditorium, First Floor, Kern County General Hospital, Bakersfield. UCLA.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. UCLA. Second and Fourth Fridays.

Neurology. 8:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

1st and 3rd Fridays, 8:30 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. UCLA.

Clinicopathologic Conference. 1st Friday, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

Internal Medicine. 2nd, 3rd, and 4th Fridays, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

MENTAL RETARDATION

February 4-16—**Mental Retardation.** UCLA. 13 days.

OBSTETRICS AND GYNECOLOGY

January 28-31—**Perinatal Biology.** USC at Kona Surf Hotel, Kona, Hawaii. Monday-Thursday.

February 6—**Prophylactic Measures for International Travel.** USC. Wednesday.

February 9-10—**Obstetrical and Gynecologic Forum.** Los Angeles Obstetrical and Gynecological Society at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. 14 hrs. $45. Contact: Miss Dee Davis, Exec. Secy., 5410 Wilshire Blvd., Los Angeles 90036. (213) 931-1621.

February 23—**New Developments in Gynecologic Cancer.** See Cancer, February 23.

March 14-15—**New Developments in Infectious Disease in Ob/Gyn.** USC. Thursday-Friday.

Continuously—**Ob/Gyn Conference.** San Joaquin General Hospital, Stockton. Mondays, 12:00-1:30 p.m. in Doctors' Dining Room. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. See Radiology and Pathology, Continuously.

Grand Rounds—Obstetrics and Gynecology

Mondays

10-11:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Tuesdays

9:00 a.m., Fifth Floor Auditorium, Room 53-105, UCLA Medical Center. UCLA.

Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Center, Sacramento. UCD.

Fridays

8:00 a.m., Auditorium, Orange County Medical Center. UCI.

10:30 a.m., Auditorium, Women's Hospital, Los Angeles County-USC Medical Center, Los Angeles. USC.

Saturdays

8:00 a.m., Executive Dining Room, University Hospital of San Diego County, San Diego. UCSD.

PEDIATRICS

January 16—**Pediatric Dermatology.** See Medicine, January 16.

January 19-20—**The Hyperactive Child: Diagnosis, Management and Current Research.** See Psychiatry, January 19-20.

January 23—**Pediatric Dermatology.** See Medicine, January 23.

January 25-27—**Pediatric Anesthesiology Conference.** See Surgery and Anesthesiology, January 25-27.

January 26—**Pediatric Urology.** See Surgery, January 26.

February 2-3—**Pediatric Urologic Seminar.** See Surgery, February 2-3.

March 7-9—**Oakland's Children's Hospital Medical Center Scientific Meeting.** Sahara Tahoe Hotel, Lake Tahoe. Thursday-Saturday. Contact: Inetta Carty, Children's Hospital Med. Ctr., 51st & Grove Sts., Oakland 94609. (415) 654-5600.

March 7-10—**Combined Southern California Pediatric Postgraduate Meeting—4th Annual.** Los Angeles Pediatric Society; Calif. Chapter 2, American Academy of Pediatrics; Childrens Hospital of L.A.; Childrens Hospital of Orange County; Southwestern Pediatric Society at Riviera Hotel, Palm Springs. Thursday-Sunday. Contact: L.A. Pediatric Society, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

Continuously—**Perinatal Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 12:30 p.m., Conference Room. Contact: Marguerite Markarian, MD, Dir. of Nurseries, Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3261.

Continuously—**Pediatric Clinical Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 8:00 a.m., Conference Room "H." Contact: Harry W. Orme, MD, Med. Dir., Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3228.

Continuously—**Preceptorships in Pediatrics.** UCSF. By arrangement.

Continuously—**Pediatric Cardiology Conference.** UCSD, Third Floor Conference Room, University Hospital. Clinical review of cases planned for the week, Tuesdays at 7:30 a.m.; Clinical review of data obtained, Fridays at 1:30 p.m. Contact: UCSD.

Continuously—**Pediatric Research Seminar.** UCSD. Mondays, 12 noon-1:00 p.m.

Continuously—**Pediatrics Clinical Conference.** San Joaquin General Hospital, Stockton. Wednesdays, 10:00-11:15 a.m., Conference Room 3. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric-Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Thursday of each month, 9:30-11:00 a.m., Conference Room 2. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric Cardiology Conference.** St. Vincent's Hospital, Los Angeles. Last Thursday of each month, 12:00 noon, Main floor conference room. Contact: Leonard M. Linde, MD, Chief, Pediatric Cardiology, St. Vincent's Hospital, 3rd and Alvarado Sts., Los Angeles.

Continuously — **Pediatric Conference.** Cedars-Sinai Medical Center, Los Angeles. Thursdays weekly, 8:30-9:30 a.m. Contact: B. M. Kagan, MD, Lebanon Hall, Cedars-Sinai Med. Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 181.

Grand Rounds—Pediatrics

Tuesdays

8:00 a.m., Children's Hospital Medical Center, Oakland.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. UCLA.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

8:30 a.m., University Hospital of San Diego County, San Diego. UCSD.

11:30 a.m., Auditorium, Pediatric Pavilion, Los Angeles County-USC Medical Center, Los Angeles. USC.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Children's Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Children's Hospital, San Francisco.

Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA.

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Pediatric Cardiology. 1st Friday of each month. 8:00 a.m., St. Vincent's Hospital, Los Angeles.

8-9:00 a.m., Lecture Hall, Children's Hospital of Los Angeles.

8:30 a.m., Room M104, Stanford University Medical Center, STAN.

8:30-9:30 a.m., alternately at St. Mary's, Children's, Mt. Zion, and Kaiser Hospitals, San Francisco.

9:30-11:00 a.m., Conference Room 2, San Joaquin General Hospital, Stockton.

Infectious Disease. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

PSYCHIATRY

January 19-20—**The Hyperactive Child: Diagnosis, Management and Current Research.** UCLA at Ackerman Union, UCLA. Saturday-Sunday.

Continuously—**Group Methods.** UCSF at VA Mental Health Services, Oakland. January 9-March 13, Wednesdays, 11:30 a.m.-1:00 p.m.

Continuously—**Adolescent Case Review.** St. Mary's Hospital, San Francisco. Wednesdays, 1:00-2:00 p.m., 3 West Conference Room. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Preceptorships in Psychiatry.** UCSF. By arrangement.

Grand Rounds—Psychiatry

Wednesdays

10:30 a.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

11:00 a.m., McAuley Institute, St. Mary's Hospital, San Francisco.

RADIOLOGY AND PATHOLOGY

January 19-20—**Ultrasound in Medical Diagnosis.** UCSF and Children's Hospital at Children's Hospital, San Francisco. Saturday-Sunday. 11 hrs. $100.

February 1-3—**Midwinter Radiological Conference—26th Annual.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. $50. Contact: James F. Mack, MD, Publicity Chr., 4500 Marloma Dr., Rolling Hills Estates 90274.

February 5-7—**Radiology.** USC at Sheraton-Harbor Island Inn, San Diego. Tuesday-Thursday.

February 9-10—**Electrophoresis.** UCSF. Saturday-Sunday.

March 1-8—**American Society of Clinical Pathologists and College of American Pathologists.** Hilton Hotel, Los Angeles. One Week. Contact: Walt Biel, College of American Pathologists, 230 N. Michigan Ave., Chicago 60601.

March 7-10—**Diagnostic Ultrasound.** UCSD at Hotel del Coronado, Coronado. Thursday-Sunday.

March 8-9—**Immunopathology of the Nucleic Acids in Rheumatic Diseases.** UCLA. Friday-Saturday.

March 9—**Abnormal Laboratory Data.** PMC. Saturday.

March 9-12—**American Association of Pathologists and Bacteriologists.** Hilton Hotel, San Francisco. Saturday-Tuesday. Contact: Am. Assn. of Pathologists and Bacteriologists, 9650 Rockville Pike, Bethesda, Md. 20014.

March 12-16—**International Academy of Pathology—63rd Annual Meeting.** Hilton Hotel, San Francisco. Tuesday-Saturday. Contact: IAP, 9650 Rockville Pike, Bethesda, Md. 20014.

March 23-24—**Diagnostic Nuclear Imaging: A Review.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

March 25-29—**Diagnostic Radiology—17th Annual Postgraduate Course.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. 33 hrs. $200.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. Mondays, 12:00 noon, Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Pathology Conference.** St. Mary's Hospital, San Francisco. 2nd and 4th Wednesdays. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Tumor Board.** St. Mary's Hospital, San Francisco. Mondays, 8:00-9:00 a.m., Clinic Building, Room 3. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Clinical Pathology Conference.** St. Mary's Hospital, San Francisco. Third Tuesday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Radiology Film Reading Sessions.** Orange County Radiology Society and Orange County Medical Center at Orange County Medical Center, Orange. 1st Tuesday of each month, September-June, 7:30-9:00 p.m. Contact: Edward J. Miller, MD, 301 Newport Blvd., Newport Beach. (714) 645-8600.

Continuously—**Cytopathology Seminars.** UCSF. 2nd Thursday of each month, September-June. 5:00-6:00 p.m. Contact: Eileen King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously — **Cytopathology Tutorial Program.** UCSF. Courses may be arranged throughout the year on the basis of individual needs and goals; fees are prorated accordingly. Arrangements should be discussed with instructor, Eileen B. King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two-part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

Continuously—**Scintillation Camera Workshop.** UCSF. Workshops provided for physicians and nuclear medicine technologists by special arrangement, limited to 30 trainees per workshop. One- or two-day intensive training periods, basic instruction in scintillation camera theory, scintographic principles and scintiphotographic interpretations. $50. Contact: UCSF.

Continuously — **Scintiphotograph Interpretation.** UCSF and Nuclear Medicine Section, Department of Radiology, UCSF. By special arrangement, designed to furnish physicians with an opportunity to participate in the daily activities of a university laboratory. Two-week training period participation in daily interpretation conferences, correlation conferences, routine training conferences. $175. Contact: UCSF.

Grand Rounds—Radiology-Pathology

Mondays

Pathology. 1:00 p.m., Sacramento Medical Center, Sacramento. UCD.

Tuesdays

Radiology. 3rd Tuesday of each month, 8:00 a.m., Bothin Auditorium, Children's Hospital and Adult Medical Center, San Francisco.

SURGERY AND ANESTHESIOLOGY

January 16—**Therapeutic Advances in Child and Adult Neurology.** LLU. Wednesday.

January 17-19 — **Neurophysiologic Basis of Rehabilitation Medicine.** UCI and American Academy of Physical Medicine and Rehabilitation at Newporter Inn, Newport Beach. Thursday-Saturday. 20 hrs. Contact: UCI.

January 17-19—**5th Mid-Winter Ophthalmology Conference.** St. Mary's Hospital and Medical Center at Morrissey Hall, St. Mary's Hospital, San Francisco. Thursday-Saturday. 12 hrs. $100. Contact: Medical Staff Secretary, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117 (415) 752-4000, ext. 101.

January 20-24—**Mid-Winter Convention for Ophthalmology and Otolaryngology—43rd Annual.** The Research Study Club at Hilton Hotel, Los Angeles. Sunday-Thursday. 32 hrs. $125. Contact: Richard Pruter, 10889 Wilshire Blvd., #1472, Los Angeles 90024. (213) 879-0143.

January 25-27—**Pediatric Anesthesiology Conference.** Childrens Hospital at Hyatt Regency Hotel, Los Angeles. Friday-Sunday. 15 hrs. $100 ($50 for military personnel, $20 for residents). Contact: Wayne Herbert, MD, Prog. Dir., 4650 Sunset Blvd., Los Angeles 90054. (213) 663-3341, ext. 2262.

January 26—**Severe Respiratory Failure.** See Medicine, January 26.

January 26—**Pediatric Urology.** UCSF at Children's Hospital, San Francisco. Saturday.

January 30-February 1—**Recent Advances in Neurology.** UCSF. Wednesday-Friday.

February 2-3—**Pediatric Urologic Seminar.** Childrens Hospital of Los Angeles. Saturday-Sunday. Contact: H. H. Edelbrock, MD, Prog. Dir., 6753 Hollywood Blvd., Suite 706, Los Angeles 90028.

February 3-6—**Theodor Billroth Course in Surgical Anatomy.** LLU. Sunday-Wednesday.

February 7-10—**Controversial Areas in Surgery of the Head and Neck.** UCSD at Vacation Village Hotel, San Diego. Thursday-Sunday. Contact: Alan M. Nahum, MD, University Hospital, 225 W. Dickinson, San Diego 92103.

February 15—**Problems of the Hip in Children.** American Academy of Orthopaedic Surgeons at Biltmore Hotel, Santa Barbara. Friday. Contact: Dean A. Smith, MD, P.O. Box 1200, Santa Barbara 93102.

February 16—**Postgraduate Refresher Course—Orthopaedic Surgery and Surgical Anatomy of Wrist and Hand.** International College of Surgeons, So. Calif. Division, at Los Angeles Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Darline Murphy, Ex. Sec., ICS, So. Calif. Div., 136 N. Brighton, Burbank 91506. (213) 846-0669.

February 17-March 1—**Temporal Bone Surgical Dissection Course.** Los Angeles Foundation of Otology, Los Angeles. 13 days. $1,000; $750 for residents. Contact: Jack L. Pulec, MD, L.A. Foundation of Otology, 2130 W. 3rd St., Los Angeles 90057.

February 20-22—**Critical Care Medicine and Circulatory Shock.** See Of Interest to All, February 20-22.

February 22—**Myasthenia Gravis.** See Medicine, February 22.

March 3—**Neuro-Ophthalmology Symposium.** CMA Ophthalmology Section at Hilton Hotel, San Francisco. Sunday. 7 hrs. $15 (includes lunch). Contact: Robert E. Christensen, MD, 800 Westwood Plaza, Los Angeles 90024.

March 7-9—**Advances in Vitreous Surgery.** UCSF. Thursday-Saturday.

March 7-10—**Western Orthopedic Association, Northern California Branch.** Ahwahnee Hotel, Yosemite National Park. Thursday-Sunday. Contact: Ida Ruth Haggerty, Exec. Secy., 145 Kimberlin Heights Dr., Oakland 94619.

(Continued on Page 44)

More than sleep.

your choice of sleep medication is wisely based on more than sleep-inducing potential

sleep with relative safety

Chronic tolerance studies have confirmed the relative safety of Dalr (flurazepam HCl); no depression of cardiac or respiratory fun was noted in patients administered recommended or higherd for as long as 90 consecutive nights.

In most instances when adverse reactions were reported, they were mild, infrequent and seldoı quired discontinuance of therapy. Morning "hang-over" with Dalmane has been relatively infrequent. I ness, drowsiness, lightheadedness and the like have been the side effects noted most frequently, particularly in the elderly and debilitated. (An initial dose of Dalmane 15 mg should be prescribed for these patients.)

sleep for 7 to 8 hou without need to repeat dosage

No sleep ı cation has been as rigorously evaluated in the sleep research laboratory as Dalmane. Insomnia pa given one 30-mg capsule of Dalmane at bedtime, on average: fell asleep within 17 minutes, had fewer ı time awakenings, spent less time awake after sleep onset, and slept for 7 to 8 hours with no need to r dosage during the night.

eep with onsistency

Dalmane has been shown to be consistently effective even during consecutive nights of administration, with no need to increase dosage.

Dalmane (flurazepam HCl) is a distinctive sleep medication—a odiazepine specifically indicated for insomnia. It is not a barate or methaqualone, nor is it related chemically to any other able hypnotic.

When your evaluation of insomnia indicates the need for a sleep cation, consider Dalmane—a single entity nonnarcotic, nonturate agent proved effective and relatively safe for relief of nnia.

DALMANE®
(flurazepam HCl)

When restful sleep is indicated

One 30-mg capsule *h.s.*—usual adult dosage
(15 mg may suffice in some patients)
One 15-mg capsule *h.s.*—initial dosage for elderly or debilitated patients.

Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening, in patients with recurring insomnia or poor sleeping habits, and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage, 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

ROCHE

ROCHE LABORATORIES
Div., Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

(Continued from Page 41)

March 14-15—**Urology Symposium—Cancer of the Genito-Urinary Tract.** STAN. Thursday-Friday.

March 16—**Postgraduate Refresher Course—Surgery and Surgical Anatomy of the Head and Neck.** International College of Surgeons, So. Calif. Division, at Los Angeles Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Darline Murphy, Ex. Sec., ICS, So. Calif. Div., 136 N. Brighton, Burbank 91506. (213) 846-0669.

March 16-17—**Los Angeles County Society of Anesthesiologists —XIX Postgraduate Assembly.** Hilton Hotel, Los Angeles. Saturday-Sunday. 15 hrs. $50 for members; $60 non-members; $50 military; $20 students, residents, interns. Contact: Virginia Connor, Exec. Secy., LACSA, 184 N. Canon Dr., Beverly Hills 90210. (213) 275-4315.

March 16-17—**Low Back Pain.** UCLA. Saturday-Sunday.

March 17-29—**Temporal Bone Surgical Dissection Course.** Los Angeles Foundation of Otology, Los Angeles. 13 days. $1,000; $750 for residents. Contact: Jack L. Pulec, MD, L.A. Foundation of Otology, 2130 W. 3rd St., L.A. 90057.

March 18-20—**G. Mosser Taylor Course in Orthopedic Surgical Anatomy—Spine.** LLU. Monday-Wednesday.

March 20-23—**Conference on Management of Trauma.** UCLA at Riviera Hotel, Palm Springs. Wednesday-Saturday.

March 23-27—**Conference on Controversial Areas in Surgery.** UCLA at Riviera Hotel, Palm Springs. Saturday-Wednesday.

March 28-30—**General Surgery.** UCSF at Hilton Hotel, San Francisco, Thursday-Saturday.

Continuously—**Basic Science Lecture Series.** Dept. of Surgery, St. Mary's Hospital, San Francisco. Mondays, 11:15 a.m.-12:15 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Mini Residencies in Orthopaedics.** STAN. Postgraduate traineeships of 4-14 days duration, as you wish. No tuition but donations accepted. Contact: Orthopaedic Division, Dept. of Surgery, Stanford.

Continuously—**Orthopedic Lecture Series.** Alternately at St. Mary's, St. Joseph's, Mary's Help, VA Martinez, Kaiser San Francisco, and Harkness Memorial Hospitals. Third Tuesday of each month, 6:00 p.m. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Orthopedic Trauma Conference.** USC at Los Angeles County-USC Medical Center. Mondays, 7:00-9:00 p.m. Contact: Dept. of Orthopedics, USC School of Med., 2025 Zonal Ave., Los Angeles 90033. (213) 225-3131.

Continuously—**Preceptorships in General Surgery.** UCSF. By arrangement.

Continuously—**Preceptorships in Neurological Surgery.** UCSF. By arrangement.

Continuously—**Preceptorships in Urology.** UCSF. By arrangement.

Continuously—**Training for Physicians in Nephrology.** CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Stewart W. Shankel, MD, LLU.

Continuously—**Surgical Anatomy.** St. Mary's Hospital, San Francisco. Mondays, 4:30 p.m., St. Mary's Hall, 2 W. Classroom. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Cline Clinic.** St. Mary's Hospital, San Francisco. Mondays, 1:30 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Morbidity and Mortality Conference.** 4th Monday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Surgical Pathology Conference.** See Radiology/Pathology, Continuously.

Continuously—**Thoracic Surgery Conference.** San Joaquin General Hospital, Stockton. Fourth Wednesday of each month, 9:00-10:30 a.m., Conference Room 1. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Medical Surgical Combined Conference.** San Joaquin General Hospital, Stockton. Second Wednesday of each month, 10:00-11:15 a.m., Conference Room 1. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Orthopaedic Audio-Synopsis Foundation.** A nonprofit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Twelve monthly c-60 cassette tapes. Annual subscription rate $72 ($36 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

Grand Rounds—Surgery

Mondays

9-10 a.m., Morrissey Hall, St. Mary's Hosiptal, San Francisco.

Tuesdays

Orthopedic Surgery. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:00-10:00 a.m., San Joaquin General Hospital, Stockton.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. UCLA.

3:30 p.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

Neurology and **Neurosurgery.** 11:00-12:15, Room 663, Science Building, UCSF.

Fridays

1:00-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego, UCSD.

Urology. 8:00 a.m., 3rd floor conference room, University Hospital of San Diego County, San Diego. UCSD.

Orthopedics. 8:00-9:00 a.m. St. Mary's Hospital, San Francisco.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA.

Orthopedics. 10:00 a.m. Auditorium of the Children's Division, Los Angeles County-USC Medical Center. The third Saturday of each month. USC.

OF INTEREST TO ALL PHYSICIANS

January 24-25—**Medicine '74.** USC. Thursday-Friday.

January 24-25—**Drug Therapy.** UCSF. Thursday-Friday.

January 30-February 2—**Physician and Hospital—5th Annual Conference.** USC at Hotel del Coronado, Coronado. Wednesday-Saturday.

February 4-5—**Occupational Skin Diseases.** UCSF. Monday-Tuesday. 11 hrs. $100.

February 6—**Prophylactic Measures for International Travel.** See Obstetrics and Gynecology, February 6.

February 6-8—**24th Annual Course for Physicians in Family Practice.** Mt. Zion Hospital, San Francisco. Wednesday-Friday.

February 9—**Setting Instructional Objectives.** PMC. Saturday. Program designed for directors of medical education.

February 11—**The Management of Cleft Palate Speech.** Rancho Los Amigos Hospital; USC; National Foundation March of Dimes, L.A. County Chapter at Rancho Los Amigos Hospital, Downey. Monday. Contact: Libby Wilson, MD, Rancho Los Amigos Hosp., 7601 E. Imperial Highway, Downey 90242. (213) 922-7454.

February 11-15—**Ski Medicine.** UCSF at Aspen, Colorado. Monday-Friday.

February 16—**Zoonotic Diseases Transmitted Between Animal and Man.** UCLA. Saturday.

February 16—**Medical Audit/PSRO.** UCLA. Saturday.

February 16—**Postgraduate Refresher Course — Orthopaedic Surgery and Surgical Anatomy of Wrist and Hand.** See Surgery, February 16.

February 18-23—**Family Practice Review.** UCI at Newporter Inn, Newport Beach. Monday-Saturday. Contact: Chuck Paul, University Extension, 424-B Computer Science Bldg., UCI, Irvine 92664.

February 20-22—**Critical Care Medicine and Circulatory Shock.** USC at Disneyland Hotel, Anaheim. Wednesday-Friday.

February 23-27—**LLU Alumni Postgraduate Convention.** Saturday-Wednesday. Contact: Wilfred J. Snodgrass, MD, Gen. Chr., 1832 Michigan Ave., Los Angeles 90033. (213) 262-2173.

February 25-March 1—**Basic Science for Clinicians—Interdepartmental Course.** STAN. Monday-Friday.

March 1—**Obesity.** USC. Friday.

March 2—**Utilization Review in Hospital Patients.** UCSF at St. Francis Hospital, San Francisco. Saturday.

March 2-6—**California Medical Association—103rd Annual Session.** Hilton Hotel, San Francisco. Saturday-Wednesday.

March 13—**New Techniques in the Care of the Critically Ill.** USC. Wednesday.

March 16—**Postgraduate Refresher Course—Surgery and Surgical Anatomy of the Head and Neck.** See Surgery, March 16.

March 16—**Psychiatry for GPs.** UCSF at Napa State Hospital, Imola. Saturday.

March 30—**Urologic Problems in General Practice.** UCD. Saturday.

Continuously—**Clinical Conferences.** UCSF and Community Hospital of Santa Cruz at Community Hospital, Santa Cruz. 2nd Wednesday of each month, Oct. 10, 1973-June 12, 1974, 11:00 a.m.-2:30 p.m. 27 hours. $50 for series; $7.50 per lecture. Jan.—Renal Disease 1974; Feb.—A Clinic on Thyroid Disease; Mar.—Fluid and Electrolyte Workshop; Apr.—Management of Acute Trauma; May—Clinic on Obesity; June—The Impotent Male and the Liberated Female.

Continuously—**Emergency Medicine.** USC. Wednesdays, 7:30-9:30 p.m.

Continuously—**Bedside Clinics.** See Medicine, Continuously.

Continuously—**Family Health Program—Southern California.** 2925 N. Palo Verde, Long Beach. Second Friday of each month. 1:00-2:00 p.m. Contact: UCI.

Continuously — **Lecture Program.** Riverside-San Bernardino Chapter, American Academy of Family Physicians and UCI at Ram's Horn Inn, San Bernardino. 3rd Thursday of each month. 7:30 p.m. Contact: UCI.

Continuously—**Lecture Program.** UCI and Orange County Chapter, American Academy of Family Physicians at Saddleback Inn, Santa Ana. 2nd Monday of each month, 7:30 p.m. Contact: UCI.

Continuously—**Hospital Lecture Program.** UCI at Anaheim Mem. Hosp.; Brea Comm. Hosp.; Fountain Valley Comm. Hosp.; Garden Park Gen. Hosp., Anaheim; Hartland Comm. Hosp., Baldwin Park; Huntington Intercomm. Hosp., Huntington Beach; Imperial Gen. Hosp., Inglewood; La Habra Comm. Hosp.; La Mirada Comm. Hosp.; Los Alamitos Gen. Hosp.; Mission Comm. Hosp., Mission Viejo; Palm Harbor Hosp., Garden Grove; Rio Hondo Mem. Hosp., Downey; San Gabriel Valley Comm. Hosp., San Gabriel; Stanton Comm. Hosp.; Studebaker Comm. Hosp., Norwalk; West Anaheim Gen. Hosp.; Westminster Comm. Hosp. Contact: UCI.

Continuously—**Professional Education Program.** Porterville State Hospital. Contact: Frank McCarry, MD, P.O. Box 2000, Porterville. (209) 784-2000.

Continuously—**Round Tables with Pacific Medical Center.** PMC and Sonoma Valley Hospital at Sonoma Valley Hospital, Sonoma. Second Monday of each month in Dining Room of the hospital, 8:00-10:00 p.m. $100 per series, $15 per session. Contact: William J. Newman, MD, P.O. Box B, Sonoma 95476. (707) 996-3621.

Continuously—**Basic Science Lecture Series.** UCSD Mondays, 4:00 p.m., third floor conference room, University Hospital of San Diego County, San Diego. Contact: UCSD.

Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $75 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

Continuously—**Medical Media Network.** Programs and study guides produced in association with faculties of major medical schools and centers throughout California. MMN administered by University Extension, UCLA. Subscriptions for all California hospitals, rental or purchase, 16 mm, super 8 mm, one-inch videotape. Provides physicians throughout the state with current educational programs in local hospitals. Consult the nearest MMN Hospital regarding time and date for viewing. Contact: Mr. David E. Caldwell, Exec. Dir., MMN, 10995 Le Conte Ave., Los Angeles 90024. (213) 825-1791.

Continuously—**Stanford Speaker's Bureau for Environmental Topics.** Stanford University Committee for Environmental Information. Provides on request speakers and programs on environmental topics. Air pollution, water pollution and water conservation issues, radiation hazards and radiation technology, pesticides and their ecological problems, medicine's responsibilities in the environmental-ecology crisis and others. Contact: STAN.

Continuously—**Stanford-Mills Memorial Hospital Continuing Education Program.** STAN at Mills Memorial Hospital, San Mateo. Tuesday-Friday weekly. Basic Science for the Clinician, Grand Rounds, Intensive Care. Contact: STAN.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

FAMILY PRACTICE

February 4-8—**Family Practice Review.** University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland. Limited to 150, registration fee $125.

April 17-19—**Sommer Memorial Lectures.** Benson Hotel, Portland.

MEDICINE

February 27 and 28—**Traumatic Emergencies.** Newport and Coos Bay. Contact: Circuit Course Program, Oregon Medical Association. 4 Credits OAFP and OMA. Tuition $20.

April 24—**Traumatic Emergencies.** Corvallis. Contact: Circuit Course Program, Oregon Medical Association. 4 Credits OAFP and OMA. Tuition $20.

OBSTETRICS AND PEDIATRICS

February 20, 21 and 22—**Pediatric and Ob Emergencies.** Klamath Falls, Medford and Roseburg. Contact: Circuit Course Program, Oregon Medical Association. 4 Credits OAFP and OMA. Tuition $20.

April 10 and 11—**Pediatric and Ob Emergencies.** Eugene and Bend. Contact: Circuit Course Program, Oregon Medical Association. 4 Credits OAFP and OMA. Tuition $20.

SURGERY

February 14—**Medical and Surgical Emergencies.** Ontario. Contact: Circuit Course Program, Oregon Medical Association. 4 Credits OAFP and OMA. Tuition $20.

February 14-16—**Chest Disease Conference.** Gleneden Beach, Salishan. Contact: Oregon Thoracic Society, 1020 S.W. Taylor Street, Portland.

March 6—**Medical and Surgical Emergencies.** Salem. Contact: Circuit Course Program, Oregon Medical Association. 4 Credits OAFP and OMA. Tuition $20.

April 3 and 4—**Medical and Surgical Emergencies.** Pendleton and LaGrande. Contact: Circuit Course Program, Oregon Medical Association. 4 Credits OAFP and OMA. Tuition $20.

WASHINGTON, MONTANA and ALASKA

REGIONAL MEDICAL PROGRAM

THIS LISTING of continuing medical education activities in Washington, Montana, and Alaska is supplied by Washington/Alaska Regional Medical Program. In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Communications Specialist, RMP, 500 University District Building, Seattle, Washington 98105.

January 17-18—**Neonatology—Fetus and the Newborn.** UW at Child Development and Mental Retardation Center, Seattle. Thursday-Friday. 13 hrs. $50. Contact: Richard L. Reimer, Asst. Dir., Cont. Med. Ed., Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

January 21-25—**Emergency Medicine for Career Emergency Physicians.** UW. Monday-Friday. 43 hrs. $200. Contact: Richard L. Reimer, Asst. Dir., E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

January 22-25—**Medical-Ski Conference 1974.** Montana Academy of Family Physicians at the Big Mountain, Whitefish, Montana. Tuesday-Friday. Contact: R. D. Buchanan, MD, P.O. Box 220, Columbia Falls, Montana 59912.

January 25-26—**Seattle Surgical Society — Annual Scientific Program.** Olympic Hotel, Seattle. Friday-Saturday. Contact: Edwin Brockenbrough, MD, Dept. of Surgery, Harborview Med. Ctr., 325 9th Ave., Seattle 98104. (206) 223-3130.

January 25-26—**Retinal Detachment and Maculopathies.** Puget Sound Academy of Ophthalmology at Washington Plaza Hotel, Seattle. Friday-Saturday. 10 hrs. $75. Contact: Charles Boylan, MD, 1601 16th Ave., Seattle. (206) 325-8500.

January 25-26—**Urology 1974.** Virginia Mason Medical Center. Friday-Saturday. 9 hrs. $50. Contact: Kenneth R. Wilske, MD, Dir., Cont. Med. Ed., Virginia Mason Med. Ctr., 111 Terry Ave., Seattle 98101. (206) 623-3700, ext. 470.

February 1-2—**Laparoscopy: Indications, Techniques, Anesthesia, Equipment.** Virginia Mason Medical Center. Friday-Saturday. 9 hrs. $250. Contact: Kenneth R. Wilske, MD, Dir., Cont. Med. Ed., Virginia Mason Med. Ctr., 111 Terry Ave., Seattle 98101. (206) 623-3700, ext. 470.

February 4-8—**Advances in Family Practice.** UW. 32½ hrs. $100. Monday-Friday. Contact: Richard L. Reimer, Asst. Dir., Cont. Med. Ed., Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

February 7-8—**New Developments in Clinical and Community Approach to the Stroke Patient.** Stroke Center, Northwest Hospital, Seattle. Thursday-Friday. 12 hrs. $30. Contact: Stroke Ctr., Northwest Hospital, 1552 N. 120th St., Seattle 98133. (206) 364-0500, ext. 557.

February 13-14—**Washington Circuit Course.** UW at St. Johns Hospital, Longview, and St. Peter Hospital, Olympia. Wednesday-Thursday. Contact: Richard L. Reimer, Asst. Dir., Cont. Med. Ed., Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

February 21-22—**Human Sexuality Counseling Workshop.** UW at Olympic Hotel, Seattle. Thursday-Friday. 13 hrs. $50. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of

Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

February 21-23—**Electromyographic Interpretation.** UW at Olympic Hotel, Seattle. Thursday-Saturday. 16½ hrs. $126. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

February 23—**Venereal Disease.** UW. Saturday. 6½ hrs. $25. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

February 28-March 1—**Symposium on Respiratory Disease—12th Annual.** UW. Thursday-Friday. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

March 1—**Colposcopy.** UW. Friday. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

March 6-7—**Washington Circuit Course.** UW at Olympic Memorial Hospital, Port Angeles, and Everett General Hospital, Everett. Wednesday-Thursday. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash. Sch. of Med., E-350 HSB, SC-50, Seattle 98195. (206) 543-1050.

March 8-9—**Problem Solving in Gastroenterology.** Virginia Mason Medical Center. Friday-Saturday. 9 hrs. $35. Contact: Kenneth R. Wilske, MD, Dir., CME, Virginia Mason Med. Ctr., 111 Terry Ave., Seattle 98101. (206) 623-3700, ext. 470.

March 14-15—**Rehabilitation Medicine Course.** UW at University Towers Hotel, Seattle. Thursday-Friday. 13 hrs. $35. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

March 14-16—**Workshop in Clinical Neurology and Neurosurgery.** W/A RMP at Holiday Inn, Everett. Thursday-Friday. Contact: Neurological Associates, Pacific & Colby Building, 1515 Pacific, Everett 98201. (206) 259-0029.

March 14-16—**North Pacific Pediatric Society—Spring Meeting.** Washington Plaza Hotel, Seattle. Thursday-Saturday. Contact: C. Patrick Mahoney, MD, The Mason Clinic, 1118 9th Ave., Seattle 98101. (206) 623-3700.

March 15-17—**Radiology of the Skeletal System.** American College of Radiology at Seattle. Friday-Sunday. 15 hrs. $200 for ACR members; $240 for non-members. Contact: ACR, 6900 Wisconsin Ave., Chevy Chase, Md. 20015.

March 16-17—**Sports Medicine Clinic—7th Annual.** W/A RMP at Sea-Tac Motor Inn, Seattle. Saturday-Sunday. 11 hrs. $50. Contact: Mr. Wayne Rasmussen, 5409 17th Ave., NW, Seattle 98107. (206) 782-3383.

March 22-23—**Dermatology: A Practical Approach to Common Problems.** Virginia Mason Medical Center. Friday-Saturday. 9 hrs. $50. Contact: Kenneth R. Wilske, MD, Dir., CME, Virginia Mason Med., Ctr., 111 Terry Ave., Seattle 98101 (206) 623-3700.

March 29—**Fetal Intensive Care.** UW at Child Development and Mental Retardation Center. Friday. 6½ hrs. $25. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

Index to The Western Journal of Medicine Advertising

Books Received 31, 32

Breon Laboratories Inc.
Bronkotabs 17

Burroughs Wellcome Co.
Empirin Compound with Codeine 21

Classified 34

Compton Foundation 34

Flint Laboratories
Synthroid 18, 19
Choloxin 23, 24

Eli Lilly Company
Kefzol 6, 7, 8
Ilosone Liquid 20

Marion Laboratories Inc.
Nico-400 ..... 36, 37

Mead Johnson Laboratories
Vasodilan 16

McNeil Laboratories
Parafon Forte 30, 31

Pharmaceutical Manufacturers Association
Prescription Ads 12, 13

PVO International
Saffola 9

Presto Food Products Inc.
Mocha Mix 27

Roche Laboratories
Dalmane 42, 43
Librium 10, 11
Valium ..... Inside Front Cover and 1

William H. Rorer, Inc.
Camalox ..... Back Cover

Sandoz Pharmaceuticals
Mellaril 14

G. D. Searle & Co.
Lomotil ..... 48 and Inside Back Cover

State Compensation Insurance Fund 22

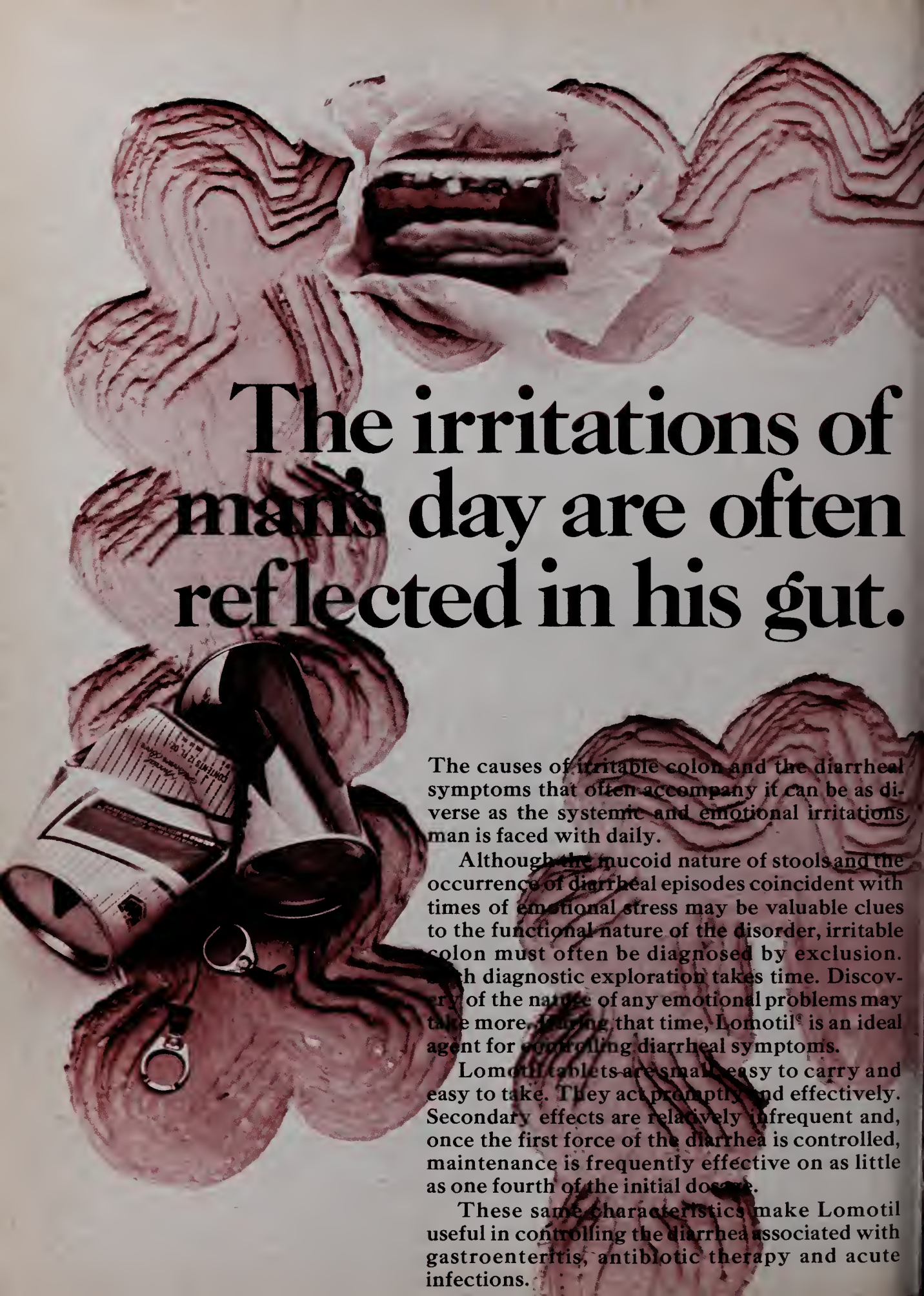
Trimont Land Co.
Northstar 2, 3

Warner-Lambert Company
Division Warner-Chilcott
Biopharmaceutics 15

Warner-Chilcott
Proloid 32, 33

Wine Institute
Enrico Caruso 5

Wyeth Laboratories
Bicillin/Wycillin 28, 29


The irritations of man's day are often reflected in his gut.
The causes of irritable colon and the diarrheal symptoms that often accompany it can be as diverse as the systemic and emotional irritations man is faced with daily.
Although the mucoid nature of stools and the occurrence of diarrheal episodes coincident with times of emotional stress may be valuable clues to the functional nature of the disorder, irritable colon must often be diagnosed by exclusion. Such diagnostic exploration takes time. Discovery of the nature of any emotional problems may take more. During that time, Lomotil® is an ideal agent for controlling diarrheal symptoms.
Lomotil tablets are small, easy to carry and easy to take. They act promptly and effectively. Secondary effects are relatively infrequent and, once the first force of the diarrhea is controlled, maintenance is frequently effective on as little as one fourth of the initial dosage.
These same characteristics make Lomotil useful in controlling the diarrhea associated with gastroenteritis, antibiotic therapy and acute infections.

Lomotil®

TABLETS/LIQUID

Each tablet and each 5 ml. of liquid contain:
diphenoxylate hydrochloride . . . 2.5 mg.
(Warning: May be habit forming)
atropine sulfate . . . . . 0.025 mg.

takes care of the gut issue in irritable colon

IMPORTANT INFORMATION: *This is a Schedule V substance by Federal law; diphenoxylate HCl is chemically related to meperidine. In case of overdosage or individual hypersensitivity, reactions similar to those after meperidine or morphine overdosage may occur; treatment is similar to that for meperidine or morphine intoxication (prolonged and careful monitoring). Respiratory depression may recur in spite of an initial response to Nalline® (nalorphine HCl) or may be evidenced as late as 30 hours after ingestion. LOMOTIL IS NOT AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN. THIS MEDICATION SHOULD BE KEPT OUT OF REACH OF CHILDREN.*

Indications: Lomotil is effective as adjunctive therapy in the management of diarrhea.

Contraindications: In children less than 2 years, due to the decreased safety margin in younger age groups, and in patients who are jaundiced or hypersensitive to diphenoxylate HCl or atropine.

Warnings: Use with caution in young children, because of variable response, and with extreme caution in patients with cirrhosis and other advanced hepatic disease or abnormal liver function tests, because of possible hepatic coma. Diphenoxylate HCl may potentiate the action of barbiturates, tranquilizers and alcohol. In theory, the concurrent use with monoamine oxidase inhibitors could precipitate hypertensive crisis.

Usage in pregnancy: Weigh the potential benefits against possible risks before using during pregnancy, lactation or in women of childbearing age. Diphenoxylate HCl and atropine are secreted in the breast milk of nursing mothers.

Precautions: Addiction (dependency) to diphenoxylate HCl is theoretically possible at high dosage. Do not exceed recommended dosages. Administer with caution to patients receiving addicting drugs or known to be addiction prone or having a history of drug abuse. The subtherapeutic amount of atropine is added to discourage deliberate overdosage; strictly observe contraindications, warnings and precautions for atropine; use with caution in children since signs of atropinism may occur even with the recommended dosage.

Adverse reactions: Atropine effects include dryness of skin and mucous membranes, flushing and urinary retention. Other side effects with Lomotil include nausea, sedation, vomiting, swelling of the gums, abdominal discomfort, respiratory depression, numbness of the extremities, headache, dizziness, depression, malaise, drowsiness, coma, lethargy, anorexia, restlessness, euphoria, pruritus, angioneurotic edema, giant urticaria and paralytic ileus.

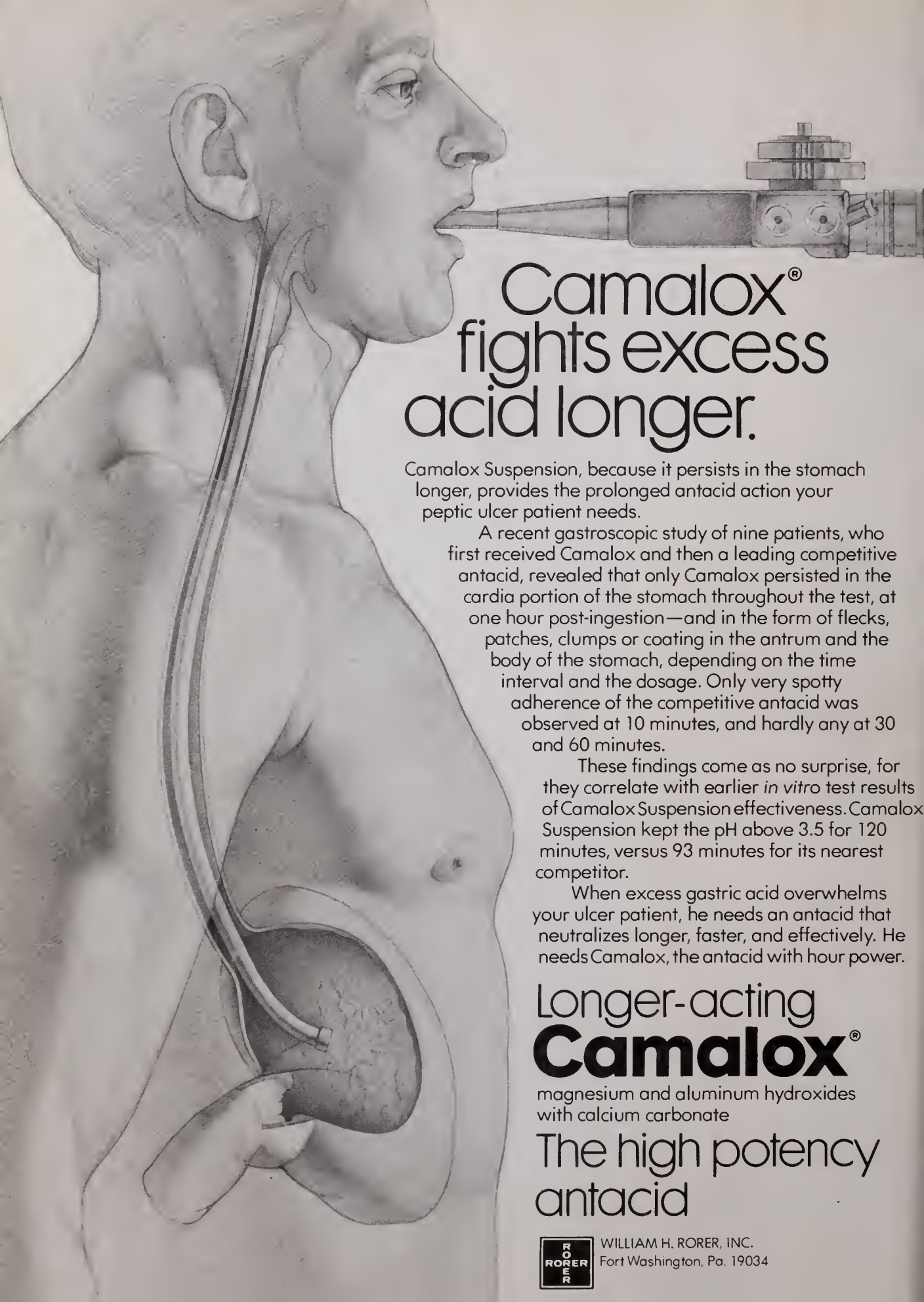
Dosage and administration: ***Lomotil is contraindicated in children less than 2 years old.*** Use only Lomotil liquid for children 2 to 12 years old. For ages 2 to 5 years, 4 ml. (2 mg.) t.i.d.; 5 to 8 years, 4 ml. (2 mg.) q.i.d.; 8 to 12 years, 4 ml. (2 mg.) 5 times daily; adults, two tablets (5 mg.) t.i.d. to two tablets (5 mg.) q.i.d. or two regular teaspoonfuls (10 ml., 5 mg.) q.i.d. Maintenance dosage may be as low as one fourth of the initial dosage. Make downward dosage adjustment as soon as initial symptoms are controlled.

Overdosage: Keep the medication out of the reach of children since accidental overdosage may cause severe, even fatal, respiratory depression. Signs of overdosage include flushing, lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, tachycardia and respiratory depression which may occur 12 to 30 hours after overdose. Evacuate stomach by lavage, establish a patent airway and, when necessary, assist respiration mechanically. Use a narcotic antagonist in severe respiratory depression. Observation should extend over at least 48 hours.

Dosage forms: Tablets, 2.5 mg. of diphenoxylate HCl with 0.025 mg. of atropine sulfate. *Liquid,* 2.5 mg. of diphenoxylate HCl and 0.025 mg. of atropine sulfate per 5 ml. A plastic dropper calibrated in increments of ½ ml. (total capacity, 2 ml.) accompanies each 2-oz. bottle of Lomotil liquid.

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Address medical inquiries to:
G. D. Searle & Co., Medical Department
Box 5110, Chicago, Illinois 60680



Camalox® fights excess acid longer.

Camalox Suspension, because it persists in the stomach longer, provides the prolonged antacid action your peptic ulcer patient needs.

A recent gastroscopic study of nine patients, who first received Camalox and then a leading competitive antacid, revealed that only Camalox persisted in the cardia portion of the stomach throughout the test, at one hour post-ingestion—and in the form of flecks, patches, clumps or coating in the antrum and the body of the stomach, depending on the time interval and the dosage. Only very spotty adherence of the competitive antacid was observed at 10 minutes, and hardly any at 30 and 60 minutes.

These findings come as no surprise, for they correlate with earlier *in vitro* test results of Camalox Suspension effectiveness. Camalox Suspension kept the pH above 3.5 for 120 minutes, versus 93 minutes for its nearest competitor.

When excess gastric acid overwhelms your ulcer patient, he needs an antacid that neutralizes longer, faster, and effectively. He needs Camalox, the antacid with hour power.

Longer-acting **Camalox®**

magnesium and aluminum hydroxides with calcium carbonate

The high potency antacid

WILLIAM H. RORER, INC.
Fort Washington, Pa. 19034

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON
MAR 1 2 1974

THE WESTERN Journal of Medicine

VOLUME 120 • NUMBER 2 **FEBRUARY 1974**

95 *Attitudes Toward Women Physicians—A Study of 500 Clinic Patients* EDGAR G. ENGLEMAN, MD

101 *Camouflage and the Augmentation Mammaplasty* JOHN Q. OWSLEY, JR, MD

105 *Side Effects of Dextroamphetamine Therapy of Hyperactive Children*
LAWRENCE M. GREENBERG, MD, SHIRLEY A. McMAHON, MD, and MICHAEL A. DEEM, PhD

110 *Neonatal Necrotizing Enterocolitis—Clinical and Radiological Features*
STEVE A. HOLT, MD, and GERALD W. FRIEDLAND, MD

116 *Family Planning Services for Adolescents and Young Adults*
WILLIAM L. MINKOWSKI, MD, MPH, ROBERT C. WEISS, MD, MPH, LAURA LOWTHER, RN, MPH, HELEN SHONICK, PHSWC, and G. A. HEIDBREDER, MD, MPH

SPECIALTY CONFERENCE

124 *Idiopathic Acute Symmetrical Polyradiculoneuritis—The Landry-Guillain-Barré Syndrome*
Participants: ROGER N. ROSENBERG, MD, and GUILLERMO MENDOZA, MD
From the weekly Pediatric Grand Rounds, University of California, San Diego, School of Medicine, University Hospital of San Diego County

MEDICAL STAFF CONFERENCE

131 *Metabolic Coma* Discussion by ROBERT T. SCOTT, M.D.

143 IMPORTANT ADVANCES IN CLINICAL MEDICINE—*Radiology*

152 EDITORIALS • *The Unconscious Patient* • *Idiopathic Polyneuritis* • *PSRO—Update 1974* • *On Justice in Medical Care*

CASE REPORTS

157 *Antacid Induction of Phosphate Depletion Syndrome in Renal Failure*
DAVID E. ABRAMS, MD, ROBERT B. SILCOTT, MD, R. TERRY, MD, THOMAS V. BERNE, MD, and BENJAMIN H. BARBOUR, MD

161 *Acute Cerebellar Ataxia of Childhood—An Unusual Case of Varicella*
PIERRE M. DREYFUS, MD, and THOMAS P. SENTER, MD

163 *Histiocytic Medullary Reticulosis in Two Chinese Women*
RODGER L. BICK, MD, and THOMPSON ADAMS, MD

167 LETTERS TO THE EDITOR

SPECIAL ESSAY

169 *A New Ethic for Medicine?* ALBERT R. JONSEN, SJ, PhD

CONTROVERSIAL ETHICAL ISSUES

174 *Birth Control, Sterilization and Abortion—Attitudes of Catholic and Protestant Clergymen in San Diego Toward Use in Families with Genetic Illness*
LAWRENCE J. SCHNEIDERMAN, MD, LORRAINE PRICHARD, PHN, SCOTT FULLER, MA, and LESLIE ATKINSON, BD, MA

180 *Book Reviews*

181 *In Memoriam*

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII; OREGON; WASHINGTON, MONTANA, AND ALASKA**
(See Advertising Page 33)

01%-EXC 013174 SUB050400T8
EXCHANGE OFF
FRANCIS A COUNTWAY LIB
10 SHATTUCK
BOSTON MA 02115

When G.I. complaints occur in the absence of organic findings, underlying anxiety may be one factor

The influence of anxiety on gastrointestinal function. Excessive anxiety and tension can adversely affect the function of any portion of the gastrointestinal system. Complaints are varied, *e.g.*, epigastric pressure, heartburn, ulcer-like pain, diarrhea, etc. A vicious circle may develop in which anxiety and G.I. disorders intensify each other.

Prime objectives of total patient therapy include: symptomatic relief, removal of apprehensions about organic disease and helping the patient understand how excessive anxiety may trigger physical

---

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON

MAR 1 2 1974

complaints. Brief counseling and the utilization of favorable factors in the patient's personality and environment can often provide needed support.

Antianxiety therapy. Antianxiety medication may prove a valuable supplement when counseling and reassurance are not sufficient to allay the patient's emotional distress and relieve his anxiety-provoked physical complaints. The agent prescribed should be both clinically effective and generally free from undesirable side effects. Librium (chlordiazepoxide HCl) meets these requirements with a high degree of consistency, and has a wide margin of safety and an excellent record of patient acceptance. The most common side effects reported have been drowsiness, ataxia and confusion, particularly in the elderly and debilitated.

Whenever anxiety is a clinically significant factor, adjunctive Librium is used concomitantly with specific gastrointestinal drugs such as anticholinergic agents. Once anxiety has been reduced to appropriate levels, treatment with Librium should be discontinued.

For relief of
excessive anxiety
adjunctive
Librium® 10 mg
(chlordiazepoxide HCl)
1 or 2 capsules t.i.d./q.i.d.

ROCHE
Roche Laboratories
Division of Hoffmann-La Roche Inc
Nutley, N.J. 07110

---

in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Supplied: Librium® Capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Libritabs® Tablets containing 5 mg, 10 mg or 25 mg chlordiazepoxide.

THE WESTERN Journal of Medicine

Since 1902 • Formerly California Medicine

OWNED AND PUBLISHED BY THE CALIFORNIA MEDICAL ASSOCIATION
731 MARKET ST. • SAN FRANCISCO, CA 94103 • TELEPHONE (415) 777-2000

editorial communications to:
MALCOLM S. M. WATTS, M.D., *Editor*

business communications to:
LYTTON O. HETLAND, *Business Manager*

. . .

LLOYD H. SMITH, JR., M.D., *Associate Editor*
ROBERT F. EDWARDS, *Managing Editor*
DAVID GREER, *Associate Managing Editor*

Editorial Board

Chairman of the Board
Malcolm S. M. Watts, San Francisco

Allergy
Norman Shure, Los Angeles
Abba I. Terr, San Francisco

Anesthesiology
Ronald L. Katz, Los Angeles

Dermatology
George F. Odland, Seattle
Rees B. Rees, San Francisco
Richard B. Stoughton, La Jolla

General and Family Practice
Robert L. Hippen, San Diego
Herbert A. Holden, San Leandro

General Surgery
Frederick M. Anderson, Reno
Richard E. Gardner, San Francisco
Lucius D. Hill, Seattle

Industrial Medicine and Toxicology
Thomas H. Milby, Berkeley

Internal Medicine
Robert J. Bolt, Davis
J. David Bristow, Portland
Marcus A. Krupp, Palo Alto
Robert G. Petersdorf, Seattle
Donald W. Petit, Los Angeles
Edgar Wayburn, San Francisco
Nathan J. Zvaifler, San Diego

Neurology
Pierre M. Dreyfus, Davis
Robert A. Fishman, San Francisco
Phillip D. Swanson, Seattle

Obstetrics and Gynecology
Ralph C. Benson, Portland
William J. Dignam, Los Angeles
Ernest W. Page, San Francisco

Ophthalmology
David O. Harrington, San Francisco
Robert S. Hepler, Los Angeles

Orthopedics
Rodney K. Beals, Portland
John A. Blosser, Oakland
Paul E. McMaster, Beverly Hills

Otolaryngology
Mansfield F. W. Smith, San Jose
Paul H. Ward, Los Angeles

Pathology
Richard L. Kempson, Stanford
Averill A. Liebow, San Diego

Pediatrics
Robert E. Greenberg, Los Angeles
William L. Nyhan, San Diego
Henry R. Shinefield, San Francisco
Paul F. Wehrle, Los Angeles

Pharmacology
Sydney M. Finegold, Los Angeles
Kenneth L. Melmon, San Francisco

Physical Medicine and Rehabilitation
Elizabeth S. Austin, Los Angeles
Glenn G. Reynolds, San Jose

Plastic Surgery
Richard L. Dakin, San Rafael
N. John Wilde, Fresno

Psychiatry
Carl Eisdorfer, Seattle
Leon J. Epstein, San Francisco
George L. Mallory, Los Angeles
Helen Tausend, Los Angeles

Public Health
J. M. Stubblebine, Sacramento
Irma M. West, Sacramento

Radiology
H. Joachim Burhenne, San Francisco
Robert B. Engle, Pasadena
Melvin M. Figley, Seattle

Thoracic and Cardiac Surgery
John E. Connolly, Irvine
Albert Starr, Portland

Urology
Thomas F. Conroy, San Mateo
Ruben F. Gittes, La Jolla

Consultants in Medical Services and Health Care
Gerald A. Besson, Sunnyvale
Paul Scholten, San Francisco

Policy Committee—Editorial Board

THOMAS N. ELMENDORF ..... Willows
STANLEY A. MOORE ..... San Diego
JOSEPH F. BOYLE ..... Los Angeles
HENRY V. EASTMAN ..... Tustin
E. KASH ROSE ..... Napa
HELEN B. WEYRAUCH ..... San Francisco
MALCOLM S. M. WATTS ..... San Francisco

Advertisements—THE WESTERN JOURNAL OF MEDICINE is published the first week of each month. Advertising copy must be received not later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee.

SALES REPRESENTATIVES: JOHN H. HARLING, INC.

EAST:
SAUL HORNIK
655 AMBOY AVENUE
WOODBRIDGE, N.J. 07095
TEL. (201) 636-7150

MIDWEST:
JOHN HARLING • JAMES ANTON
18 SO. MICHIGAN AVE.
CHICAGO, ILL. 60603
TEL. (312) 641-0755

WEST:
MELVIN B. TYLER
731 MARKET ST.
SAN FRANCISCO, CA. 94103
TEL. (415) 777-2000

Copyright, 1974, by the California Medical Association.

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the non-commercial purpose of scientific or educational advancement.

Subscription prices, $8 ($9 for foreign countries); student subscription $4; single copies 80 cents.

Volumes begin with the first of January and the first of July. Subscriptions may commence at any time.

Change of Address—Requests for change of address should give both the old and new address.

CONTRIBUTIONS OF SCIENTIFIC AND ORIGINAL ARTICLES

Responsibilities for Statements and Conclusions in Original Articles—Authors are responsible for all statements, conclusions and methods of presenting their subjects. These may or may not be in harmony with the views of the editorial staff. It is aimed to permit authors to have as wide latitude as the general policy of the Journal and the demands on its space may permit. The right to reduce, revise or reject any manuscript is always reserved.

Exclusive Publication—Articles are accepted for publication on condition that they are contributed solely to this Journal. Ordinarily contributors will be notified within 60 days if a manuscript is accepted for publication. Every effort will be made to return unused manuscripts.

Length of Articles—Ordinarily articles should not exceed 3,000 words (approximately 5 printed pages). Under exceptional circumstances only will articles of over 4,000 words be published.

Manuscripts—Manuscripts should be typewritten, double spaced and the original typescript plus one copy submitted.

Illustrations—Ordinarily publication of 2 or 3 illustrations accompanying an article will be paid for by THE WESTERN JOURNAL OF MEDICINE. Any number beyond this might have to be paid for by the author.

References—Should conform to the following order: name of author, title of article, name of periodical, with volume, inclusive pages, month and year—i.e.: Lee GS: The heart rhythm following therapy with digitalis—In theory and practice. Arch Int Med 44:554-562, Dec 1942. They should be listed in the order in which they are cited in the text, numbered in sequence and punctuated as above.

Reprints—Reprints must be paid for by the author at established standard rates.

CONTRIBUTIONS OF "LETTERS TO THE EDITOR"

The Editorial Board will be glad to receive and consider for publication letters containing information of general interest to physicians or presenting constructive criticisms on issues of the day.

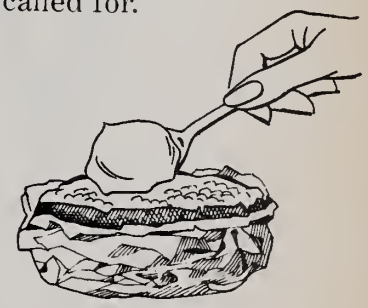
"Entered as second class matter at the post office in San Francisco and additional mailing offices under the Act of March 3, 1879." Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized August 10, 1918.

Good news for saturated fat watchers...

ew Matey® Sour Dressing. Low in saturated fat, Cholesterol free!

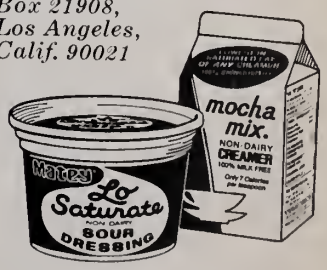
Imagine. A sour dressing you can feel free to recommend. One that gives all the satisfaction of the one you had to restrict, but that has a relative saturated fat to total fat of only 18% as compared to over 50% for dairy sour cream. What's more, delicious new Matey® Non-Dairy Lo Saturate Sour Dressing is made from a blend of liquid safflower and soybean oils (the only one that is) and is *completely cholesterol free.*

If your patients are bored with a saturated fat restricted diet, they'll love the way new Matey can liven up their menu. Great for dips, on baked potatoes, fruit salad or cooking ...anywhere a sour dressing is called for.



New Matey. You'll find it in your grocer's dairy case now. Better yet, write for a free supply of coupons so you and your patients can sample it free. We'll also send you a complete data sheet for your files.

Presto Food Products, Inc.
Box 21908,
Los Angeles,
Calif. 90021



Made by the makers of Mocha Mix®...the non-dairy creamer that's lowest in saturated fat. Both available in larger sizes for hospitals and institutions.

THE NATURAL WAY

For more than thirty years PREMARIN (Conjugated Estrogens Tablets, U.S.P.) has been prepared with natural equine estrogens exclusively—without synthetic estrogen supplements. For more than thirty years it has provided the complete estrogen complex in the proportions found in its natural source. And for more than thirty years PREMARIN has enjoyed an unparalleled record of clinical efficacy and acceptance.

PREMARIN. The only estrogen preparation available that contains natural estrogens exclusively and als meets all U.S.P. specifications for conjugated estrogens. Assurance of quality for you and your patients.

PREMARIN . . . naturally.

BRIEF SUMMARY
(For full prescribing information, see package circular.)
PREMARIN®
(Conjugated Estrogens Tablets, U.S.P.)

Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.
Warnings: Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.
Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Pre-existing uterine fibromyomata may increase in size while using estrogens; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.
Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest
Dosage and Administration: PREMARIN should be administered cyclically (3 weeks of daily estrogen and 1 week off) for all indications except selected cases of carcinoma and prevention of postpartum breast engorgement.

Menopausal Syndrome—1.25 mg. daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg. to 1.25 mg. daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg. daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg. to 1.25 mg. or more daily, depending upon the tissue response of the individual patient. Administer cyclically.
How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)

No. 865—Each *purple* tablet contains 2.5 mg., in bottles of 100 and 1,000.

No. 866—Each *yellow* tablet contains 1.25 mg., in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 867—Each *red* tablet contains 0.625 mg., in bottles of 100 and 1,000.

No. 868—Each *green* tablet contains 0.3 mg., in bottles of 100 and 1,000. 7352

PREMARIN®

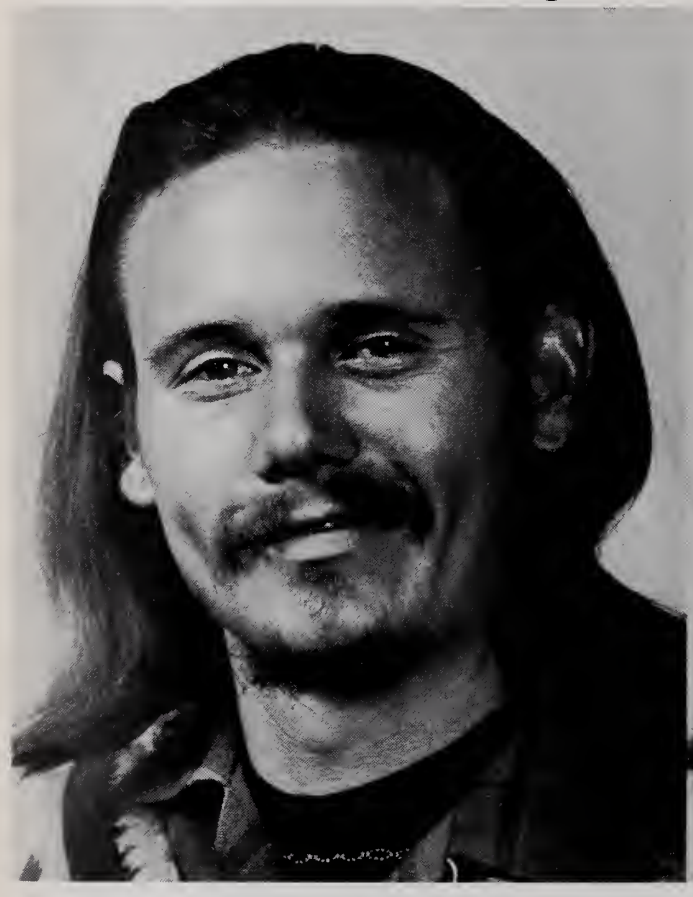
BRAND OF CONJUGATED ESTROGENS TABLETS, U.S.P.

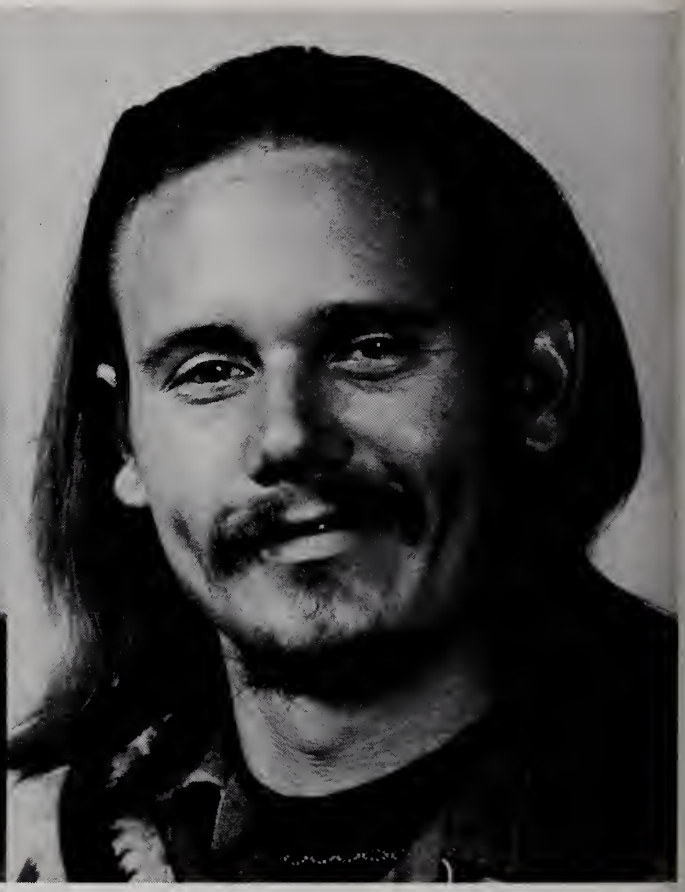
CONTAINS ONLY NATURAL ESTROGENS ...NO SYNTHETICS OR SUPPLEMENTS

Ayerst

AYERST LABORATORIES
New York, N.Y. 10017

Case history #2





Charles' well-being comes first.

Charles' being well comes first.

Charles Havard is a quadriplegic. He is also a rehabilitation counselor for the Alhambra Open Door Clinic. And only recently, he was selected as *Rehabilitant of the Year* by the Pasadena Department of Rehabilitation.

It all began on January 23, 1962. While working as a physical education instructor for the Y.M.C.A., Charles sustained a serious injury to his cervical cord after falling from the horizontal bar during a gymnastics demonstration. The result: quadriplegia.

State Fund entered the case immediately. Following emergency treatment, he was transferred to Rancho Los Amigos in Downey for comprehensive care.

From February 23 until he was discharged in early August, Charles was visited regularly by the State Fund rehabilitation staff. With their guidance and his own tremendous courage, along with the help of others who really cared, Charles made rapid progress in adjusting to his disability.

Soon after his release, he entered college. He earned both Bachelor and Master of Arts degrees, leading to his present counselling job. Charles certainly earned his success. State Fund helped.

Conserving your human resources is our only business

STATE COMPENSATION INSURANCE FUND

situation:
Elderly...doesn't get out much anymore...whole world slowed down.
constipation:
Poor eating habits...often, on various constipating drugs...inactive, frequently debilitated...weakened muscles ...sluggish, atonic bowel. Result—in many oldsters—constipation.
laxation:
Gentle, predictable and easy-to-take SENOKOT Tablets or Granules. Taken at bedtime, they usually induce comfortable evacuation in the morning. Leave your older patient feeling more like getting up and around.
Supplied: SENOKOT Tablets (small, easy-to-swallow)—Bottles of 50 and 100. SENOKOT Granules (delicious, cocoa-flavored)—4, 8 and 16 ounce (1 lb.) canisters.
Senokot
(standardized senna concentrate)
Tablets/Granules
a natural laxative
Purdue Frederick
A7D31 128673
© COPYRIGHT 1973. THE PURDUE FREDERICK COMPANY/NORWALK CONN. 06856

When low back pain* interferes...

Help relieve pain, restore mobility with

PARAFON FORTE® Tablets

PARAFLEX® (chlorzoxazone)† 250 mg.; TYLENOL® (acetaminophen) 300 mg.

*This drug has been evaluated as "possibly" effective for this indication.

See brief summary of prescribing information on facing page for Indications, Contraindications, Warnings, Precautions and Adverse Reactions.

© McN 73

ARAFON FORTE® Tablets
lp relieve pain, store mobility and op pain-spasm edback by providing:

n salicylate analgesic equal to rin for relief of pain,[1,2] yet unlikely use the gastric irritation,[2,3] gic reactions[2] or increased bleeding [4] associated with aspirin therapy.

a skeletal muscle relaxant vn in extensive clinical studies to be ul in a variety of low back rders[5-7]* but which is not an nistamine or tranquilizer derivative is unlikely to produce a quilizing or sedative effect.[8]

cations Based on a review of this drug by the National demy of Sciences-National Research Council and/or other mation, FDA has classified the indications as follows:

ssibly" effective for the relief of severe skeletal muscle pain spasm when associated with acute disorders of the lower k (including acute exacerbations of chronic conditions).

indications: Sensitivity to either component.

gs: *Usage in Pregnancy*—Use in woman of child-bearing al only when potential benefits outweigh possible risks.

tions: Exercise caution in patients with known allergies or f drug allergies. If a sensitivity reaction or any signs or symp- ggestive of liver dysfunction are observed, the drug should ped.

e Reactions: Occasionally, drowsiness, dizziness, lighthead- malaise, overstimulation or gastrointestinal disturbances noted. rarely, allergic-type skin rashes, petechiae, ecchy- angioneurotic edema or anaphylactic reactions. In rare in- *Paraflex* (chlorzoxazone) may possibly have been associ- th gastrointestinal bleeding. While *Paraflex* (chlorzoxazone) lorzoxazone-containing products have been suspected as e cause of hepatic toxicity in approximately eighteen pa- was not possible to state that the dysfunction was or was not duced.

dult Dosage: Two tablets q.i.d

d: Scored, light green tablets, imprinted "McNEIL"— f 100.

ces: **1.** Batterman, R.C., and Grossman, A.J.: Fed Proc. *14*:316, Goodman, L.S., and Gilman, A., ed The Pharmacological Basis of utics, ed 4 New York, The Macmillan Company, 1970 **3.** Vickers, stroint Endosc. *14* 94, 1967 **4.** Mielke, C.H., Jr., and Britten A.F.H. J Med *282* 1270, 1970 (Corresp.) **5.** Vernon, W.G. Curr Therap 801, 1972 **6.** Scheiner, J.J. Curr Therap. Res *14* 168, 1972 **7.** M Curr Therap Res *15*:248, 1973 **8.** Friend, D.G. Clin Pharma- *5* 871, 1964

†U.S. Patent No. 2,895,877

NEIL McNeil Laboratories, Inc.
Fort Washington, Pa. 19034

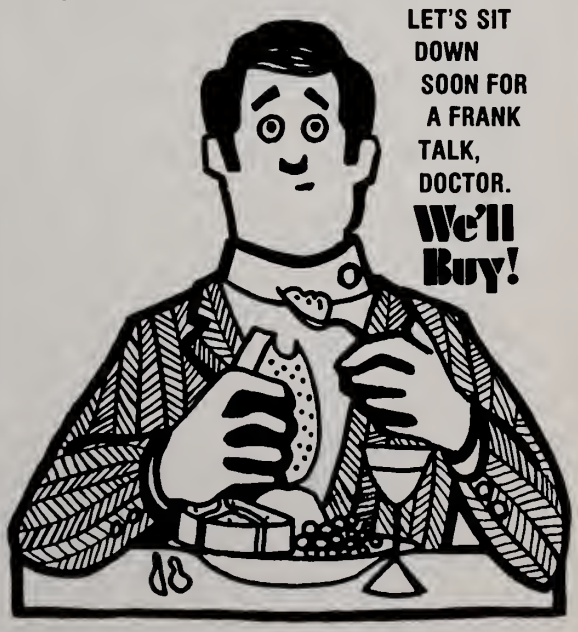
When was the last time you made money at lunch, Doctor?

Right off we'll assure you of at least a break even—*we'll buy lunch!*

Beyond that, our service to nearly 2,000 doctors should qualify us as an organization with an understanding and appreciation of the problems of the professional man.

Simply, and there is much more to it, we are a unique firm, organized to provide the health care professions with the means to free-up capital and then prudently invest to produce additional wealth.

But we can't recommend until we know you and you know us. We feel that we have a program to meet every need—but first we must work with you to isolate that need.



medi-fund

The Medi-Fund Corporation
525 Spruce Street
San Francisco, Ca. 94118

Please tell me more about these services

- ☐ Profit center lease
- ☐ New equipment lease
- ☐ New practice lease
- ☐ New equipment rental
- ☐ Tax shelter investments
- ☐ Purchase leaseback

Name _____

Address _____

City _____ State _____ Zip _____

In Gonorrhea

Injection WYCILLIN®

(sterile procaine penicillin G suspension) Wyeth

Penicillin in large doses remains the drug of choice in therapy of gonorrhea. Among penicillins, first choice recommended by the national Center for Disease Control for parenteral therapy of uncomplicated gonorrhea is aqueous procaine penicillin G.

Administration of 4.8 million units together with 1 gram oral probenecid, preferably given at least 30 minutes prior to injection, is recommended in treatment of uncomplicated gonorrhea.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reaction.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings.")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated) — Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid preferably given at least 30 minutes prior to injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists or more days following initial therapy and smear or culture remain positive. Follow-up treatment consists of 4.8 million units. I. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *gonorrhoeae.* Follow-up treatment consists of 4.8 million units daily 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test syphilis at the time of diagnosis. Patients with gonorrhea who a have syphilis should be given additional treatment appropriate to stage of syphilis.

Composition: Each TUBEX® disposable syringe 2,400,000 ur (4-cc. size) contains procaine penicillin G in a stabilized aque suspension with sodium citrate buffer, and as w/v approximal 0.7% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpy lidone, 0.01% propylparaben and 0.09% methylparaben. The n tiple-dose 10-cc. vial contains per cc. 300,000 units procaine p cillin G in a stabilized aqueous suspension with sodium citrate bu and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulos mg. polyvinylpyrrolidone, 0.5 mg. sorbitan monopalmitate, 0.5 polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylpara and 1.2 mg. methylparaben.

Denise has VD

Let's keep it from getting around

Actual new cases of infectious syphilis apparently reached the 100,000 mark during the past year; new cases of gonorrhea, more than 2.5 million. That VD is rampant again is due, in large part, to the multiple contacts of teenagers like Denise.

By administering adequate doses of the recommended types of penicillin, you can usually cure VD in the beginning stages. And destroy another link in the chain of infection.

In Syphilis

Injection

BICILLIN® Long-Acting (sterile benzathine penicillin G suspension) Wyeth

Benzathine penicillin G...a drug of choice recommended by the national Center for Disease Control in all stages of syphilis and in preventive treatment after exposure.

Administration of 2.4 million units (1.2 million in each buttock) of benzathine penicillin G usually • cures most cases of primary, secondary and latent syphilis with negative spinal fluid • helps break chain of infection • minimizes chance of immediate reinfection.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular benzathine penicillin G.—Venereal infections: Syphilis, yaws, bejel and pinta.

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: 2,400,000 units in 4-cc. single dose disposable syringe. Each TUBEX disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. Units benzathine penicillin G (as active ingredient), 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. polyvinylpyrrolidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Wyeth Laboratories • Philadelphia, Pa. 19101

When the asthmatic can anticipate the attack

Bronkotabs®

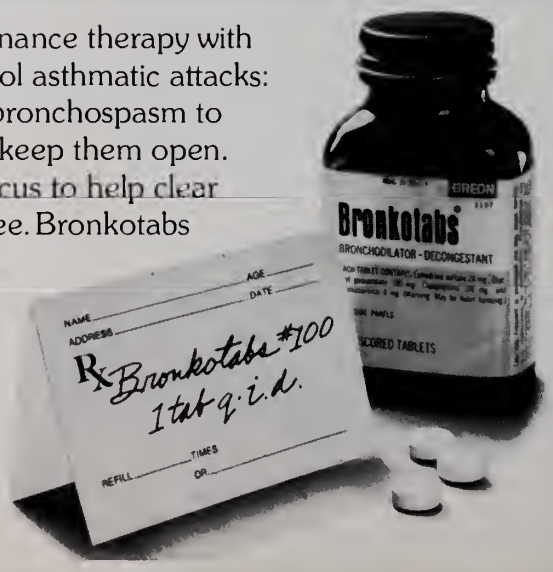
Each tablet contains ephedrine sulfate 24 mg; theophylline 100 mg; glyceryl guaiacolate 100 mg; phenobarbital 8 mg (warning: may be habit-forming).

can help forestall or relieve it

Why day to day maintenance therapy with Bronkotabs helps control asthmatic attacks:

Bronkotabs relieves bronchospasm to open airways and help keep them open.

Bronkotabs thins mucus to help clear the tracheobronchial tree. Bronkotabs decongests bronchiolar mucosa to improve the passage of air. Economical long-term therapy.



PRECAUTIONS AND ADVERSE EFFECTS: Sympathomimetic side effects are minimal, and there are none of the dangers or side effects associated with steroid therapy. However, frequent or prolonged use may cause nervousness, restlessness or sleeplessness. Should be used with caution in the presence of hypertension, heart disease or hyperthyroidism. Drowsiness may occur. Ephedrine may cause urinary retention, especially in the presence of partial obstruction, as in prostatism.

DOSAGE: Adults, one tablet every three or four hours, four or five times daily. Children over six, one-half the adult dose. Children under six, as directed.

SUPPLIED: Bottles of 100 and 1,000 tablets.

BREON

BREON LABORATORIES INC.
90 Park Avenue, New York, N.Y. 10016

situation:

Impaired cardiac status . . . straining at stool may be hazardous. . .

constipation:

Restricted physical activity . . . often, major changes in customary daily routine . . . constipating medications. . .

laxation:

SENOKOT Tablets or Granules, taken at bedtime, generally induce effective, yet comfortable evacuation in the morning . . . help avoid straining.

Supplied: SENOKOT Tablets (small, easy-to-swallow) — Bottles of 50 and 100. SENOKOT Granules (delicious, cocoa-flavored) — 4, 8 and 16 ounce (1 lb.) canisters.

Senokot Tablets Granules
(standardized senna concentrate)

a natural laxative

PURDUE FREDERICK
© 1974 THE PURDUE FREDERICK COMPANY
NORWALK, CONN 06856 136874

A NEW INJECTABLE ANTIBIOTIC

Please see last page for prescribing information

Lilly introduces a new cephalosporin

Kefzol™

cefazolin sodium

Ampoules, equivalent to 250 mg., 500 mg., and 1 Gm. of cefazolin

Its major areas of indication:

espiratory tract infections

ue to susceptible strains of *Diplococcus neumoniae, Klebsiella* species, *Hemophilus nfluenzae, Staphylococcus aureus* (penicillin-ensitive and penicillin-resistant), and group A eta-hemolytic streptococci (Injectable enzathine penicillin is considered to be the rug of choice in the treatment and prevention f streptococcal infections, including the rophylaxis of rheumatic fever.)

enito-urinary tract infections

ue to susceptible strains of *Escherichia coli, roteus mirabilis, Klebsiella* species, and some rains of *Enterobacter* and enterococci

kin and soft-tissue infections

ue to susceptible strains of *Staph. aureus* enicillin-sensitive and penicillin-resistant) and roup A beta-hemolytic streptococci and other rains of streptococci

ee prescribing information for additional ndications and susceptible organisms.

Some of its major features:

therapeutic serum levels

peak serum levels of 37.9 and 63.8 mcg./ml. respectively were obtained one to two hours following 500-mg. and 1-Gm. I.M. doses of cefazolin

antibacterial urinary concentrations

peak urine concentrations of approximately 2,400 and 4,000 mcg./ml. respectively were obtained following I.M. doses of 500 mg. and 1 Gm.

bile and synovial-fluid levels

levels approximately one-half those of serum concentrations

flexibility of administration

usual adult dosage—500 mg. to 1 Gm. t.i.d. or q.i.d.

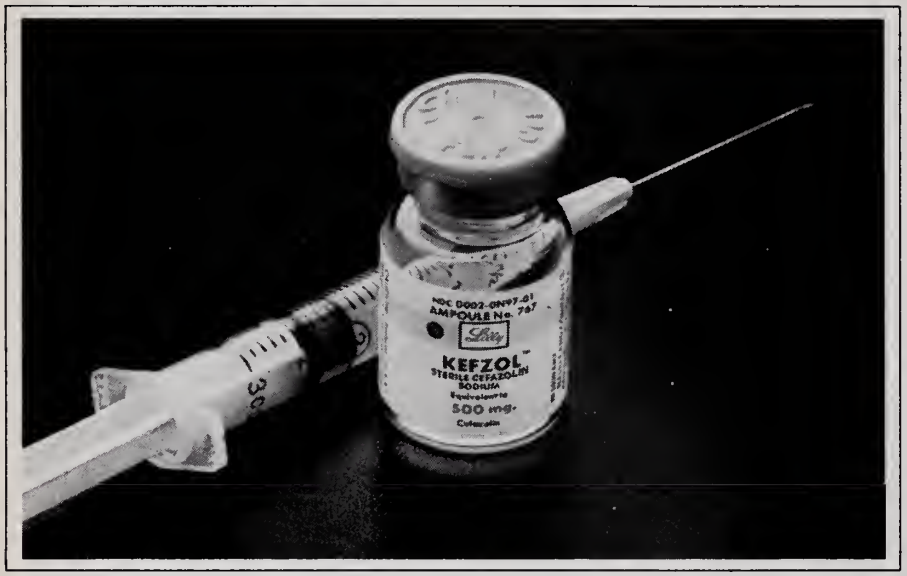
Kefzol is contraindicated in patients with known allergy to cephalosporins and should be given with great caution to penicillin-allergic patients.

Please see following page for summary of prescribing information.

301623

Kefzol™
cefazolin sodium

a new injectable antibiotic



Description: Kefzol™ (cefazolin sodium, Lilly) is a semisynthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1,3,4-thiadiazol-2-yl) thio]methyl}-8-oxo7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

Actions: *Microbiology*— In-vitro tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell-wall synthesis. Kefzol is active against the following organisms in vitro:

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Diplococcus pneumoniae
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole-positive *Proteus (Pr. vulgaris, Pr. morganii, Pr. rettgeri)* are resistant. Methicillin-resistant staphylococci, *Serratia, Pseudomonas, Mima,* and *Herellea* species are almost uniformly resistant to cefazolin.

Indications: Kefzol is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *D. pneumoniae, Klebsiella* species, *H. influenzae, Staph. aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci

Injectable benzathine penicillin is considered to be the drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

Kefzol is effective in the eradiction of streptococci from the nasopharynx; however, data establishing the efficacy of Kefzol in the subsequent prevention of rheumatic fever are not available at present.

Genito-urinary tract infections due to *Esch. coli, Pr. mirabilis, Klebsiella* species, and some strains of *Enterobacter* and enterococci

Skin and soft-tissue infections due to *Staph. aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci

Bone and joint infections due to *Staph. aureus*

Septicemia due to *D. pneumoniae, Staph. aureus* (penicillin-sensitive and penicillin-resistant), *Pr. mirabilis, Esch. coli,* and *Klebsiella* species

Endocarditis due to *Staph. aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Kefzol™ (cefazolin sodium, Lilly).

Contraindication: KEFZOL IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

Warnings: IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics, including Kefzol, cautiously and then only when absolutely necessary. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Usage in Pregnancy— Safety of this product for use during pregnancy has not been established.

Usage in Infants— Safety for use in prematures and infants under one month of age has not been established.

Precautions: Prolonged use of Kefzol may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When Kefzol is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false-positive reaction for glucose in the urine of patients on Kefzol has occurred with Clinitest® tablets solution.

Adverse Reactions: The following reactions have been reported:

Hypersensitivity—Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood—Neutropenia, leukopenia, thrombocythemia, and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal—Transient rise in SGOT, SGPT, BUN, and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment.

Gastro-Intestinal—Nausea, anorexia, vomiting, diarrhea, and oral candidiasis (oral thrush) have been reported.

Other—Pain at the site of injection after intramuscular administration has occurred, some with induration. Phlebitis at the site of injection has been noted.

Administration and Dosage: Kefzol may be administered intramuscularly or intravenously after reconstitution.

Dosage— In adults, usual dosage for mild gram-positive infections is 250 to 500 mg. of Kefzol every eight hours. In acute uncomplicated urinary tract infections, a dosage of 500 mg. every eight hours is usually adequate. In moderate or severe infections, the usual adult dosage is 500 mg. to 1 Gm. of Kefzol every six to eight hours. Kefzol has been administered in dosages of 6 Gm. per day in serious infections such as endocarditis. Kefzol may be used in patients with reduced renal function with the following dosage adjustments: In patients with mild to moderate impairment (creatinine clearance of 60-40 ml./min.), 60 percent of the normal daily dose given in divided doses q. 12 h. should be sufficient. In patients with moderate impairment (creatinine clearance of 40-20 ml./min.), 25 percent of the normal daily dose given in divided doses q. 12 h. should be sufficient. In patients with marked impairment (creatinine clearance of 20-5 ml./min.), 10 percent of the normal daily dose given q. 24 h. should be adequate. All dosage recommendations apply after an initial loading dose of 500 mg.

In children, a total daily dosage of 25 to 50 mg. per Kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg. per Kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of Kefzol in these patients is not recommended.

How Supplied: Ampoules Kefzol™ (cefazolin sodium, Lilly), Sterile, equivalent to 250 or 500 mg. cefazolin, 5-ml. size, rubber-stoppered; equivalent to 1 Gm. cefazolin, 10-ml. size, rubber-stoppered.

[102

Lilly

Additional information availa to the profession on request

Eli Lilly and Company
Indianapolis, Indiana 462

301589

Bio-Science Reports

TSH by RIA at BSL

Bio-Science Laboratories adds still another valuable laboratory aid for the diagnosis of thyroid disorders: serum Thyroid Stimulating Hormone (TSH) by radioimmunoassay (RIA). The exquisite sensitivity of the RIA technic permits the detection of normal levels of TSH, which have been reported to average about 4.0 microunits/ml with a range of "non-detectable to 10 microunits/ml" (Hershman, J. M. and Pittman, J. A., New Eng. J. Med. *285:*997, 1971).

The RIA method for TSH was pioneered by Utiger and Odell *et al.* in 1965. We are employing Hershman's modification of this method. Hershman and Pittman have reviewed the utility of the RIA of serum TSH in man (Annals Intern. Med. *74:*481, 1971) and have emphasized its usefulness both for establishing the diagnosis of primary hypothyroidism and for differentiating it from hypothyroidism secondary to hypopituitarism. TSH levels above normal are strongly suggestive of the existence of primary hypothyroidism and may in fact be the most sensitive index of this disease.

Quotable Quotes

FOLATE:

". . . the results support the suggestion that red cell folate provides a better assessment of folate status than does serum folate." (J. Clin. Path. *22:*212, 1969).

". . . serum folate assay is a valuable routine test in patients who have a macrocytic anaemia and low serum vitamin B_{12}." (J. Clin. Path. *24:*244, 1971).

Note: We offer both serum and red cell folate measurements. As a matter of fact, if you order a red cell folate, our report includes both serum and red cell values.

RUBELLA:

"HAI (hemagglutination inhibition) antibodies are the first to be detectable, around 12-15 days after exposure; they rise rapidly and reach peak titers within one to three weeks . . . . , and the CF response is delayed 10-14 days after onset, with maximal titers being attained after three or four weeks." (J. Infect. Diseases *123:*640, 1971).

More New Tests at Your Service

Some of the newer tests currently available from Bio-Science Laboratories are listed below:

- Amebic (E. histolytica) antibodies
- Aldosterone by RIA
- Anti-DNA antibodies
- Complement decay rate
- Cyclic AMP by RIA
- Digoxin or digitoxin in serum, by RIA
- Estradiol by RIA
- Gamma glutamyl transpeptidase
- Gastrin by RIA
- Hemoglobin S, screening
- Histidine
- Human somatomammotropin (Human placental lactogen)
- Lecithin: sphingomyelin ratio in amniotic fluid
- Measles antibody by CF
- Mumps antibody detection
- Parathyroid hormone by RIA
- Phenotyping of Lipoproteins: Indirect confirmation of II, III, IV
- Red cell enzyme screening
- Renin, by RIA or bioassay
- Thyroid microsomal antibody
- TSH by RIA
- T_3 level in serum by RIA
- Vitamin E (α-tocopherol)

Bio-Science is a full-service lab that can handle all your clinical lab needs. Try us.

25 YEARS

Main Lab: 7600 Tyrone Ave., Van Nuys, California 91405

Philadelphia Branch: 116 So. Eighteenth St., Philadelphia, Pa. 19103

Bio-Science Laboratories
7600 Tyrone Avenue
Van Nuys, California 91405 Dept. B B
or
116 So. Eighteenth St.
Philadelphia, Pa. 19103

Gentlemen: Please send me, without obligation:

☐ A copy of your Handbook of Specialized Diagnostic Laboratory Tests

☐ A lab pack containing a small supply of postage-paid mailing containers and Fee Schedule

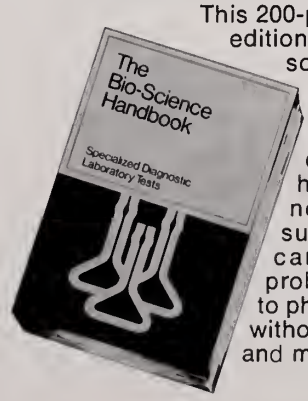
Name

Address

City State Zip

FREE

HANDBOOK OF SPECIALIZED DIAGNOSTIC LABORATORY TESTS



This 200-page book, now in its tenth edition, is a uniquely informative source to keep you up-to-date on the newer laboratory tests, such as serum TSH, available to clinicians. You will find it a handy reference guide for normal values and quick summations on tests which can aid in your diagnostic problems. Copies are available to physicians and lab personnel without obligation. Simply fill out and mail this coupon.

Synthroid®
(sodium levothyroxine)

the smooth road to thyroid replacement therapy.

Synthroid is T4. It provides your patients with what is needed for complete thyroid replacement therapy.

Free Tab-Minder sample packages available from Flint Professional Services Department.

Indications: SYNTHROID (sodium levothyroxine) is specific replacement therapy for diminished or absent thyroid function resulting from primary or secondary atrophy of the gland, congenital defect, surgery, excessive radiation, or antithyroid drugs. Indications for SYNTHROID (sodium levothyroxine) **Tablets** include myxedema, hypothyroidism without myxedema, hypothyroidism in pregnancy, pediatric and geriatric hypothyroidism, hypopituitary hypothyroidism, simple (nontoxic) goiter, and reproductive disorders associated with hypothyroidism. SYNTHROID (sodium levothyroxine) **for Injection** is indicated for intravenous use in myxedematous coma and other thyroid dysfunctions where rapid replacement of the hormone is required. The injection is also indicated for intramuscular use in cases where the oral route is suspect or contraindicated due to existing conditions or to absorption defects, and when a rapid onset of effect is not desired.

Precautions: As with other thyroid preparations, an overdosage of SYNTHROID (sodium levothyroxine) may cause diarrhea or cramps, nervousness, tremors, tachycardia, vomiting and continued weight loss. These effects may begin after four or five days or may not become apparent for one to three weeks. Patients receiving the drug should be observed closely for signs of thyrotoxicosis. If indications of overdosage appear, discontinue medication for 2-6 days, then resume at a lower dosage level. In patients with diabetes mellitus, careful observations should be made for changes in insulin or other antidiabetic drug dosage requirements. If hypothyroidism is accompanied by adrenal insufficiency, such as Addison's Disease (chronic adrenocortical insufficiency), Simmonds's Disease (panhypopituitarism) or Cushing's syndrome (hyperadrenalism), these dysfunctions must be corrected prior to and during SYNTHROID (sodium levothyroxine) administration. The drug should be administered with caution to pa with cardiovascular disease; developm chest pains or other aggravations of card cular disease requires a reduction in dosa

Contraindications: Thyrotoxicosis, acute m dial infarction. **Side effects:** The effects o THROID (sodium levothyroxine) therapy ar in being manifested. Side effects, when t occur, are secondary to increased rates o metabolism; sweating, heart palpitation or without pain, leg cramps, and weigh Diarrhea, vomiting, and nervousness hav been observed. Myxedematous patient heart disease have died from abrupt inc in dosage of thyroid drugs. Careful obse of the patient during the beginning of a roid therapy will alert the physician to a toward effects.

It has been shown that *Synthroid* (T_4) converts to T_3 at the cellular level to supply metabolic needs.[1,2]

1 *Synthroid* is T_4.

2 Because T_4 converts to T_3 at the cellular level, it provides full thyroid replacement at maintenance doses.[1,2]

3 T_4 hormone content is controlled by chemical assay.

4 *Synthroid* is assayed chemically; no biologic test is necessary to measure potency.

5 *Synthroid* provides predictable results when used with current thyroid function tests.

6 *Synthroid* is the most prescribed brand name of thyroid in the U.S. and Canada.

7 Sodium levothyroxine in *Synthroid* tablets is chemically pure. It does not contain any animal gland parts.

8 When stored properly, *Synthroid* has a longer shelf life than desiccated thyroids.

9 On a daily basis, *Synthroid* is cost competitive with other thyroid products.

The smooth road to thyroid replacement therapy.

Synthroid®
(sodium levothyroxine)

most cases with side effects, a reduction of e followed by a more gradual adjustment d will result in a more accurate indication patient's dosage requirements without the rance of side effects.

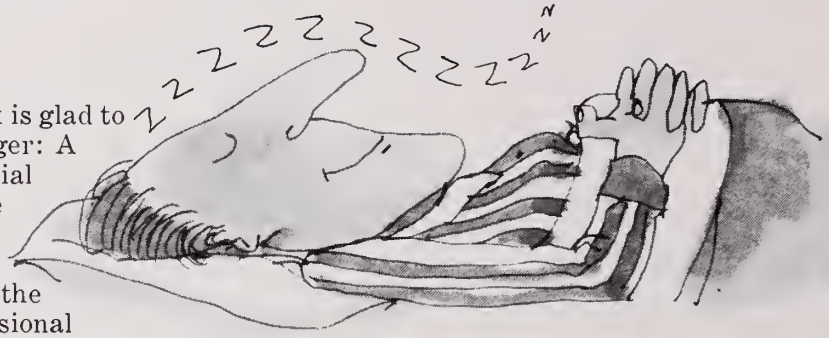
e and Administration: The activity of mg. SYNTHROID (sodium levothyroxine) T is equivalent to approximately one grain , U.S.P. Administer SYNTHROID tablets ingle daily dose. In hypothyroidism with- yxedema, the usual initial adult dose is g. daily, and may be increased by 0.1 mg. 30 days until proper metabolic balance is ed. Clinical evaluation should be made ly and PBI measurements about every 90 Final maintenance dosage will usually from 0.2-0.4 mg. daily. In adult myxedema, g dose should be 0.025 mg. daily. The dose may be increased to 0.05 mg. after two weeks and to 0.1 mg. at the end of a second two weeks. The daily dose may be further increased at two-month intervals by 0.1 mg. until the optimum maintenance dose is reached (0.1-1.0 mg. daily).

Supplied: Tablets: 0.025 mg., 0.05 mg., 0.1 mg., 0.15 mg., 0.2 mg., 0.3 mg., 0.5 mg., scored and color-coded, in bottles of 100, 500, and 1000. Injection: 500 mcg. lyophilized active ingredient and 10 mg. of Mannitol, U.S.P., in 10 ml. single-dose vial, with 5 ml. vial of Sodium Chloride Injection, U.S.P., as a diluent. SYNTHROID (sodium levothyroxine) **for Injection** may be administered intravenously utilizing 200-400 mcg. of a solution containing 100 mcg. per ml. If significant improvement is not shown the following day, a repeat injection of 100-200 mcg. may be given.

1. Braverman, L. E., Ingbar, S. H., and Sterling, K.: Conversion of Thyroxine (T_4) to Triiodothyronine (T_3) in Athyreotic Human Subjects, J. Clin. Invest. 49:855-64, 1970.
2. Surks, M. I., Schadlow, A. R., and Oppenheimer, J. H.: A New Radioimmunoassay for Plasma L-Triiodothyronine: Measurements in Thyroid Disease and in Patients Maintained on Hormonal Replacement. J. Clin. Invest. 51:3104-13, 1972.

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015

Our prescription for your practice: Take MediManager and get plenty of sleep.



Security Pacific Bank is glad to introduce MediManager: A comprehensive financial management package for the physician and dentist.

MediManager is the most complete professional service package ever offered to physicians and dentists. It's designed to be of help in (1) patient billing and collection, (2) patient credit, (3) equipment financing, (4) acquisition of facilities, and (5) estate management.

MediManager features a computerized patient billing service with insurance form preparation capabilities. It offers remittance banking and payroll help, as well as a unique patient credit plan that gives you prompt payment for your services. MediManager provides commercial and real estate loans, equipment loans and leasing, auto leasing and locational assistance. Finally, it can help you with trusts, pension plans and profit-sharing programs.

Ask your branch manager about MediManager: Something special from Security Pacific Bank.

SECURITY PACIFIC BANK
SOMETHING SPECIAL

© 1973 SECURITY PACIFIC NATIONAL BANK MEMBER FDIC

Banana-Flavored Donnagel®-PG

The civilized solution to the age-old problem of diarrhea.

The evolution of Donnagel®-PG:

Kaolin and pectin to provide demulcent-detoxicant effects.

Belladonna alkaloids for antispasmodic benefits.

Powdered opium, the therapeutic equivalent of paregoric—without the unpleasant taste—to promote the production of formed stools and lessen the urge.

And a delicious banana flavor good enough for the most discriminating tastes.

All together in the evolutionary discovery that's the best-tasting way yet to treat acute, non-specific diarrheas.

Donnagel®-PG

Donnagel with paregoric equivalent.
Each 30cc. contains:

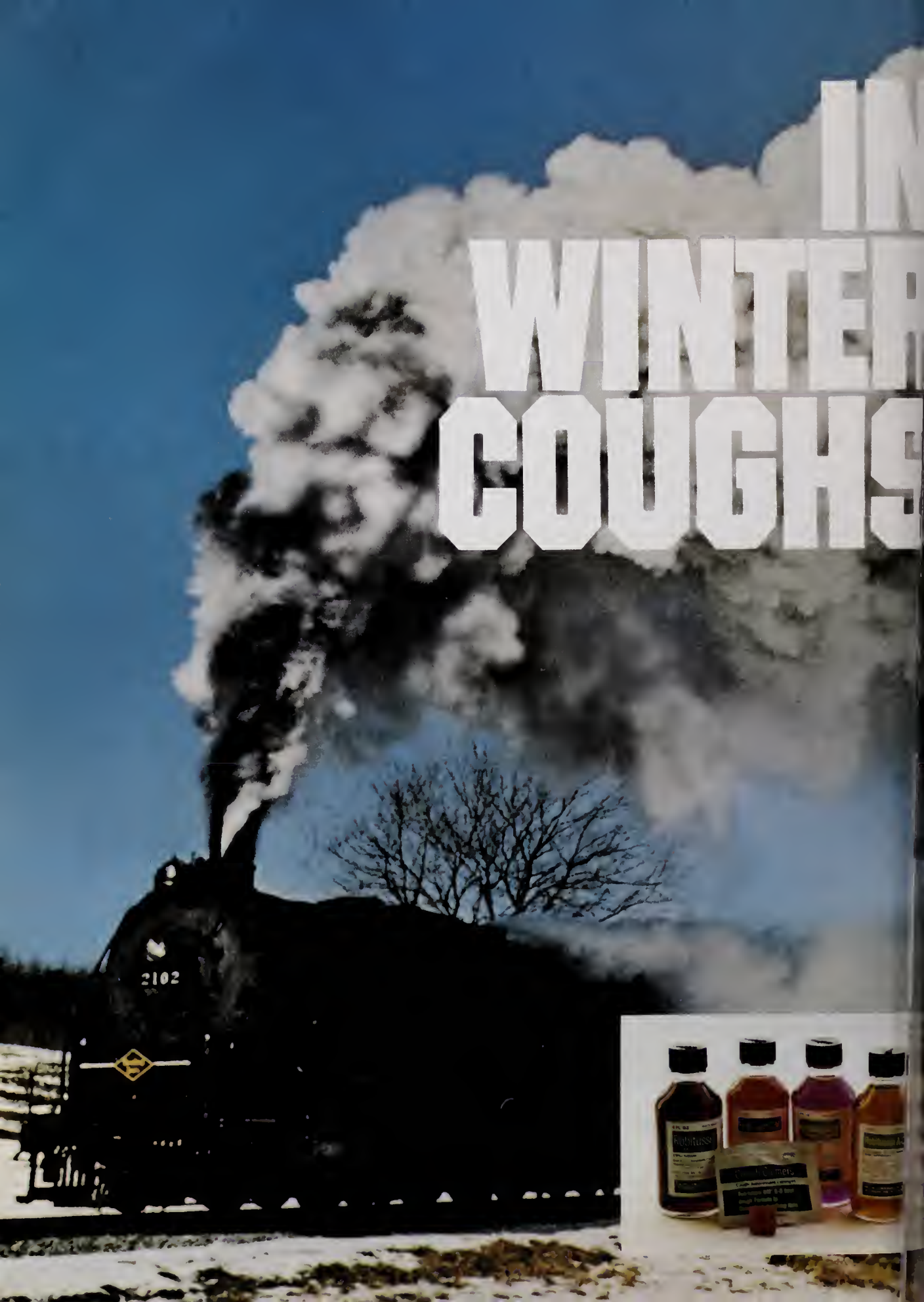
Kaolin	6.0 g.
Pectin	142.8 mg.
Hyoscyamine sulfate	0.1037 mg.
Atropine sulfate	0.0194 mg.
Hyoscine hydrobromide	0.0065 mg.
Powdered opium, USP. (equivalent to paregoric 6 ml.) (warning: may be habit forming)	24.0 mg.
Sodium benzoate (preservative)	60.0 mg.
Alcohol, 5%	

℞ Available on oral prescription or without prescription in compliance with applicable state and local law.

A·H·ROBINS

Chimp courtesy of Ringling Brothers & Barnum & Bailey Combined Shows, Inc

A. H. Robins Company, Richmond, Virginia 23220


IN
WINTER
COUGHS
2102

CLEAR THE TRACT WITH THE ROBITUSSIN® LINE

The coughing season is here again. Time to rely on the four Robitussins and Cough Calmers to help clear the lower respiratory tract. All contain glyceryl guaiacolate, the efficient expectorant that works systemically to help increase the output of lower respiratory tract fluid. The enhanced flow of less viscid secretions soothes the tracheobronchial mucosa, promotes ciliary action, and makes thick, inspissated mucus less viscid and easier to raise. Available on your prescription or recommendation.

For coughs of colds and "flu"

ROBITUSSIN®

Each 5 cc. contains:
Glyceryl guaiacolate ..... 100 mg.
Alcohol, 3.5%

For severe coughs

ROBITUSSIN A-C® C

Each 5 cc. contains:
Glyceryl guaiacolate ..... 100 mg.
Codeine phosphate ..... 10.0 mg.
(warning: may be habit forming)
Alcohol, 3.5%

Non-narcotic for 6-8 hr. cough control

ROBITUSSIN-DM®

Each 5 cc. contains:
Glyceryl guaiacolate ..... 100 mg.
Dextromethorphan hydrobromide ..... 15 mg.
Alcohol, 1.4%

Robitussin-DM in solid form for "coughs on the go"

COUGH CALMERS®

Each Cough Calmer contains:
Glyceryl guaiacolate ..... 50 mg.
Dextromethorphan hydrobromide ..... 7.5 mg.

Relieves cough, clears sinuses and nasal passages—keeps them "drip-dry" but not bone dry

ROBITUSSIN-PE®

Each 5 cc. contains:
Glyceryl guaiacolate ..... 100 mg.
Phenylephrine hydrochloride ..... 10 mg.
Alcohol, 1.4%

...the Robitussin® ...a Tract" Formulation ...t reats Your Patient's ...vual Coughing ...d

	Expectorant-Demulcent	Cough Suppressant	Long-Acting (6-8 hours)	Nasal, Sinus Decongestant	Non-Narcotic
...USSIN®	●				●
...USSIN A-C®	●	●			
...USSIN-DM®	●	●	●		●
...USSIN-PE®	●			●	●
...G CALMERS®	■	■	■		■

...andy chart as a guide in selecting the formula that provides the benefits you want for your patient.

A·H·ROBINS

A. H. Robins Company, Richmond, Virginia 23220

Classified Advertisements

The rate for each insertion is **$2.50 per line** (average six words per line) **with five line minimum.**

Box number charge: $1.50 each month.

Classified display rates $25.00 per inch.

Copy for classified advertisements should be received not later than **the fifth of the month preceding issue.** • Classified advertisers using Box Numbers forbid the disclosure of their identity. Your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the rules of the Advertising Committee.

CLASSIFIED ADVERTISEMENTS ARE PAYABLE IN ADVANCE

PHYSICIANS WANTED

FAMILY PRACTITIONER — 21-doctor multi-specialty group located in beautiful coastal city ½ way between S.F. and L.A. Full partnership offered in six months. Contact Administrator, San Luis Medical Clinic, 1235 Osos Street, San Luis Obispo, CA 93401, (805) 543-4800.

INTERNIST—21-doctor multi-specialty group located ½ way between S.F. and L.A. in beautiful coastal city with many recreational advantages. Full partnership offered in six months. Contact Administrator, San Luis Medical Clinic, 1235 Osos Street, San Luis Obispo, CA 93401, (805) 543-4800.

LOS ANGELES-ORANGE COUNTIES — Growing HMO needs more General Practitioners, Pediatricians, Orthopods, OB/GYN's and ENT. Competitive salaries, regular increases and tax-sheltered fringe benefits. Two newly opened medical centers. Send your curriculum vitae to: Frank Eaton, MD, Medical Director, Family Health Program, Room 2419, 2925 Palo Verde, Long Beach, CA 90815.

SAN DIEGO INTERNIST needed immediately. Rare opportunity to take over thriving and established practice, in a large modern completely equipped office, with no investment necessary. Central location, ample parking, close to hospitals. Box 9371 Western Journal of Medicine, 731 Market St., S.F., CA 94103.

CA-FP PHYSICIAN FOR SEMI-RURAL COMMUNITY (50,000)—40 minutes North of San Francisco. Good climate and recreation. Excellent hospital. Congenial medical community pledged to assist in establishing practice to include housing, officing, equipment, and financial and social adjustment. Administrator, Hillcrest Hospital, Box 2010. Petaluma, CA 94952, (707) 762-2706.

PSYCHIATRIST to direct a comprehensive Community Mental Health Center in Southern California. Flexible, innovative, brilliant, but pragmatic. Program development, consultation and coordination, evaluation, grants procurement. Contact the Administrator, San Fernando Valley Community Mental Health Center. 9017 Reseda Boulevard, Northridge, CA (213) 885-7788.

NEONATOLOGIST for position on faculty of the Department of Pediatrics at UCLA-Harbor General Hospital. Opening is at Professor level to direct a Division of Perinatal Medicine. Send Curriculum Vitae to Delbert A. Fisher, MD, Acting Chairman, Department of Pediatrics, Harbor General Hospital, 1000 West Carson Street, Torrance, CA 90509. We are an Affirmative Action Employer.

INTERNIST, GENERALIST AND UROLOGIST, State Veterans Home and Hospital. Salary depending upon training, experience and position to be filled. Excellent retirement plan and other benefits. Located one hour from San Francisco in beautiful Napa Valley. Call or write John P. Preston, Administrator, Phone (707) 944-2422.

PHYSICIANS WANTED

OPHTHALMOLOGIST — ASSOCIATE NEEDED — Board certified or eligible—position available 3/1/74—Salary plus percentage and fringe benefits. Albert Tashma, MD, Inc., 7080 Hollywood Boulevard, Los Angeles, CA 90028, (213) 466-4285.

CARDIOLOGY-NEONATOLOGIST for position on faculty of the Department of Pediatrics at Harbor General Hospital. Send Curriculum Vitae to Delbert A. Fisher, MD, Acting Chairman, Department of Pediatrics, Harbor General Hospital, 1000 West Carson Street, Torrance, CA 90509. We are an Affirmative Action Employer.

SITUATIONS WANTED

DERMATOLOGIST — Board certified — California license. Age 40—healthy. Experienced in academic dermatology and private practice. Desires relocation in San Diego area. Will consider any reasonable opportunity. Available within six months. Please give full details in first letter. Box No. 9372, Western Journal of Medicine, 731 Market Street, S.F., CA 94103.

NUCLEAR MEDICINE—ABNM certified, ABIM eligible, physician with 11 years experience in Nuclear Medicine as director of laboratories in private hospitals, seeks full-time directorship of Nuclear Medicine Lab or association with group for practice of Nuclear or Nuclear and Internal Medicine. Box 9373, c/o The Western Journal of Medicine, 731 Market Street, S.F., CA 94103.

FREE LANCE MEDICAL WRITER

FREE LANCE MEDICAL WRITER— author of five books and numerous articles will help you prepare your writing for lay publication, John Fried, 741½ Levering Avenue, Los Angeles, CA 90024.

GENERAL PRACTITIONER

To work with 4 other GP's and 1 Internist in Clinic. Salary to be negotiated. Eventual partnership. Two hospitals nearby. Ideal community, 50,000. 45 miles San Francisco. Send resume or call collect Fairfield Clinic (707) 425-2975, Fairfield, CA.

PHYSICIAN

Non-resident positions with a background in general medicine for evening work in a program of eight youth clinics within Los Angeles County. General medical and counseling help is provided primarily to adolescents and young adults in a caring, non-judgmental setting. Sessions run between three and four hours. The pay scale is $50 for the first hour and one-half, $25 per hour thereafter, with a maximum of $125 for 4½ hours. If interested, please contact:

William L. Minkowski, MD
(213) 225-3115, Ext. 79911

PSYCHIATRIST

Dynamic opportunity available for a Child Psychiatrist at Henry Ford Hospital. We are a major University affiliated, 1100 bed hospital, out-patient clinic (33 specialty fields), with several suburban and inner-city satellite clinics. This is a full time position which offers an excellent salary and fringe benefits program. For further information please contact:

DR. H. vonBRAUCHITSCH
DEPARTMENT OF PSYCHIATRY
HENRY FORD HOSPITAL
2799 W. GRAND BLVD.
DETROIT, MICHIGAN 48202

An Equal Opportunity Employer

(Continued on Page 30)

PHYSICIAN

Hospital residents in Pediatrics, Internal Medicine, Psychiatry, Family Medicine or in other specialties (if you have prior general medical experience) for early evening work in youth clinics. These clinics provide general medical and counseling services primarily for adolescents and young adults in eight locations within Los Angeles County. The emphasis is on caring, non-judgmental attitudes and high quality (non-academic) treatment. Sessions usually 3 to 4 hours. The pay varies with years of experience from $12.31 to $14.90 per hour. The clinical experience is unique, patients are deeply grateful for services offered and important community health needs are being met in this program. If interested, please contact:

William L. Minkowski, MD
(213) 225-3115, Ext. 79911

PSYCHIATRIC RESIDENCY

Three years fully approved program in a large, University affiliated General Hospital. We provide closely supervised training in dynamic psychiatry, child psychiatry, medicolegal experience and basic neurology. Salary to $15,000. plus benefits. For further details and consideration, submit your resume to:

DR. ROBERT SCHOPBACH
DIRECTOR OF PSYCHIATRIC TRAINING
HENRY FORD HOSPITAL
2799 W. GRAND BLVD.
DETROIT, MICHIGAN 48202

An Equal Opportunity Employer

SAN FRANCISCO STATE UNIVERSITY

MEDICAL ORIENT-PACIFIC STUDY-TRAVEL PROGRAM

Following American Academy of Pediatrics 43rd Annual Meeting at San Francisco

San Francisco State University Continuing Education courses for credit or audit. A program of overseas studies and on-site observations of how the medical profession in the areas visited copes with the socio-economic-cultural conditions related to medical matters.

These courses are designed to contribute professional values which only overseas on-site studies and observations can provide doctors. Therefore, doctors may qualify for tax deductions, but should consult their accountants.

All prices below include roundtrip airfares, top first class hotels, sightseeing, transfers, tips, etc., escorted.

JAPAN-HONG KONG
OCT. 25 THRU NOV. 10—17 DAYS, for only $799
Tokyo, Kyoto, and Hong Kong. Price includes roundtrip airfares based on the Northwest Airlines chartered jet flight being 100% filled.

ORIENT
OCT. 24 THRU NOV. 16—24 DAYS, for only $1499
Tokyo, Nikko, Osaka, Kyoto, Seoul, Taipei, Manila, Oenspasar (Bali), Singapore, Bangkok, and Hong Kong.

SOUTH PACIFIC
OCT. 24 THRU NOV. 16—24 DAYS, for only $1499
Papeete, Auckland, Waitomo, Rotorua, Queenstown, Milford Sound, Mt. Cook, Christchurch, Melbourne, Canberra, Sydney, Nandi, Yanuca Island, Apia, and Pago Pago.

For Details, Apply:
SFSU STUDY-TRAVEL PROGRAM
c/o Institute of Int'l. Studies & Seminars
526 Grand Avenue; Oakland, California 94610

TRAVEL ARRANGEMENTS BY
HOWARD TOURS, INC.

Must vasodilators and therapy for other diseases come into conflict?

not if the vasodilator is

VASODILAN®
(ISOXSUPRINE HCl)

the compatible vasodilator... no treatment conflicts reported

The cerebral or peripheral vascular disease patient often has coexisting disease[1] which calls for another drug along with his vasodilator. It may be a hypoglycemic, miotic, antihypertensive, diuretic, anticoagulant, corticosteroid, or coronary vasodilator.

Vasodilan is not incompatible with any of these drugs—no treatment conflict has been reported. And, unlike other vasodilators, Vasodilan has not been reported to affect carbohydrate metabolism, liver function, or intraocular pressure—or to complicate treatment of diabetes, hypertension, peptic ulcer, glaucoma, or liver disease.

In fact, there are no known contraindications to the use of Vasodilan in recommended oral doses, other than that it should not be given in the presence of frank arterial bleeding or immediately postpartum.

1. Gertler, M. M., et al.: Geriatrics *25*:134-148 (May) 1970.

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.
3. Threatened abortion.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.

Dosage and Administration: 10 to 20 mg. three or four times daily.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Adverse Reactions: On rare occasions, oral administration of the drug has been associated in time with the occurrence of severe rash. When rash appears, the drug should be discontinued. Occasional overdosage effects such as transient palpitation or dizziness are usually controlled by reducing the dose.

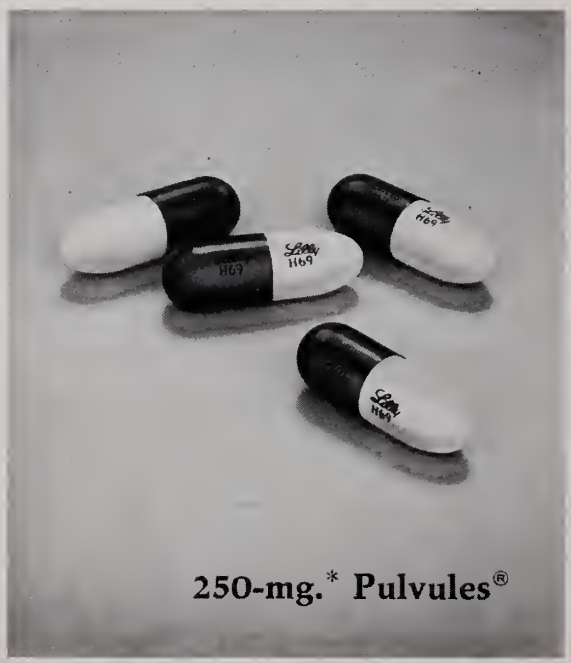
Supplied: Tablets, 10 mg.—bottles of 100, 1000, 5000 and Unit Dose; 20 mg.—bottles of 100, 500 and Unit Dose.

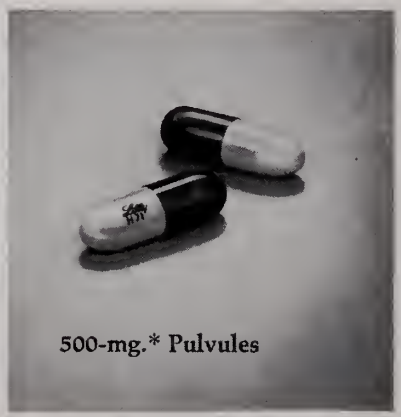
© 1973 MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA 47721 U.S.A. 734017

Mead Johnson LABORATORIES

Keflex®
cephalexin monohydrate

it makes sense





*Equivalent to cephalexin.

Additional information available to the profession on request.

Eli Lilly and Company • Indianapolis, Indiana 46206

Lilly

400123

THE WESTERN
Journal of Medicine

Refer to: Engleman EG: Attitudes toward women physicians—A study of 500 clinic patients. West J Med 120:95-100, Feb 1974

Attitudes Toward Women Physicians

A Study of 500 Clinic Patients

EDGAR G. ENGLEMAN, MD, *Bethesda, Maryland*

A questionnaire was administered to 500 clinic patients and their replies about men and women physicians were analyzed. Ninety-six percent stated that the typical doctor is a man, and 78 percent expressed a preference for a male doctor. A significant number of patients said they would be unwilling to discuss certain subjects with a woman doctor or to follow her advice. Women physicians were considered less competent and less experienced than their male counterparts.

Attitudes toward women doctors were correlated with patients' sex, age, ethnicity, occupation, and chief complaint. Most impressive statistically were the negative attitudes of Spanish-speaking patients and the positive responses of obstetrics and gynecology patients and black women patients. Patients who had previously consulted women physicians were more favorable toward them, suggesting that increased exposure may lead to reduced prejudice.

THE DOCTOR-PATIENT RELATIONSHIP is crucial to the delivery of health care in that patients who trust their physicians are more likely to give candid histories and to follow medical advice. One potential barrier to this relationship, sex bias on the part of patients, is the subject of this report. To date, the possibility of prejudice against physicians by patients, based on the sex of the physician, has not been systematically explored.[1] This study compared the attitudes of a sample of clinic patients toward male and female doctors and examined the sociocultural determinants of patient attitudes toward female physicians. These results are part of a larger study of the effects of certain of the physician's biosocial attributes (sex, age, ethnicity, style of dress, hair style) on the patient's attitude toward the physician.

Method

A questionnaire was administered to 500 outpatients at three general medical clinics in New York City's west side. Each clinic was hospital-

From the School of Medicine, Columbia University College of Physicians and Surgeons, and Department of Medicine, University of California, San Francisco, School of Medicine.

The author is a research associate at the National Heart and Lung Institute of the National Institutes of Health, Bethesda, Md. At the time the study was made he was a student at Columbia University College of Physicians and Surgeons, New York City.

This investigation was supported in part by Public Health Service General Research Support Grant 5S01-FR-05449.

Reprint requests to: Editorial Office, 998-M, Department of Medicine, University of California, San Francisco, San Francisco, CA 94143.

based and served a variety of ethnic groups, including black and Spanish-speaking patients. Patient care in all three clinics was provided by a training house staff. In none of the clinics did patients choose their doctors.

Interviewing took place from 9 AM to 5 PM during a six-week period. Four experienced interviewers, all women 30 to 45 years of age, were employed. Two were white and English-speaking, one was black and English-speaking, one was Puerto Rican and bilingual. They did not wear uniforms or white coats. For each interview, the interviewer was directed by hospital personnel to the patient who had arrived most recently and who, therefore, had longest to wait before seeing a doctor. This technique minimized the frequency of refusals (2 percent), as well as interrupted (10 percent) and incomplete (5 percent) interviews, and helped maintain good relations between interviewers and hospital staff. Interrupted and incomplete questionnaires were analyzed insofar as possible.

The questionnaire required 30 to 40 minutes to administer and consisted of 130 questions that had been field-tested in a pilot study of 60 patients. Twenty-five items relating to physician gender were interspersed throughout the schedule. In most instances the questionnaire was administered in relative privacy in a room provided by the clinic. Patients were asked to participate in "an opinion survey about doctors." The interviewer explained to patients that, while she had permission to be in the clinic, she was neither responsible to nor employed by the clinic and that no clinic personnel would have access to the results. Strictest confidentiality was adhered to; the names of patients were not recorded.

Results

Patient attitudes toward male and female physicians

That medicine continues to be perceived as a male-dominated profession was reflected by the sample, 96 percent of whom felt that the "typical" doctor was a man. Seventy-eight percent said that, if given a choice, they preferred a male physician, 13 percent preferred a female physician, and only 9 percent had no preference. Fifty-one percent of the sample declared the doctor's gender to be the single most important attribute in a long list of biosocial characteristics including age, ethnicity, religion, neatness, dress and, for men physicians, the presence of long hair, beard, or mustache. Female physicians were considered less competent and less experienced than their male counterparts, but were also seen as cleaner, more emotional, more trustworthy, and more concerned about poor patients.

Patients were asked a series of questions about two hypothetical doctors, one of whom fulfilled the patient's preference with regard to gender and one of whom did not. Regardless of preferred gender, patients "confronted" by a doctor of the undesired sex claimed to be less willing to discuss their medical histories, to ask advice on sexual problems, to take prescribed medicines, or to submit to hospitalization (all $p<0.005$ by chi-square analysis for each variable).

Sociocultural determinants of attitudes toward female physicians

Table 1 shows selected demographic characteristics of the 500 patients interviewed. Other characteristics (income, education, third-party payment scheme, number of visits to doctor each year, whether a private physician was the primary physician, patient's view of seriousness of illness, how patient selected clinic, whether patient had previously attended clinic) did not yield significant differences in attitudes toward women physicians.

Women were, on the whole, more favorably inclined toward female physicians (Table 1). For example, a higher percentage of women than men preferred a woman physician as their regular doctor ($p<0.001$) and preferred to discuss personal problems with a female physician ($p<0.001$).

Younger patients were more favorably disposed toward female physicians, although the results were not wholly one-sided. Higher percentages of patients younger than age 30 expressed a preference for female doctors ($p<0.001$) and preferred to confide in female doctors about personal problems ($p<0.001$). On the other hand, when asked to predict their reactions to hypothetical physicians of either sex, young patients were far more hesitant to seek advice on sexual problems ($p<0.001$) and less willing to take prescribed medicines than were older patients ($p<0.001$).

Many more Spanish-speaking patients (70 percent from Puerto Rico; 15 percent each from Cuba and the Dominican Republic) exhibited a negative attitude toward female physicians than whites who, in turn, responded less favorably than blacks. Thus, for example, a higher percent-

TABLE 1.—*Significant Sociocultural Variables* in Attitudes of Patients Toward Female Physicians*

Variable	Respondents		Doctor Preference			Competence of Female Doctors†			
	N	Percent of Total	Percent Male	Percent Female	Percent Either	Percent More	Percent Same	Percent Less	Percent Don't Know
Sex:									
Male	182	36.4	83.9	5.6	10.6	16.1	50.0	25.0	8.9
Female	318	63.6	75.2	16.6	8.3	20.8	46.3	27.5	5.4
Age:									
30 or younger	209	41.9	68.1	20.3	11.6	20.3	44.4	29.5	5.8
31 to 60	211	42.3	84.2	7.7	8.1	20.1	50.2	23.4	6.2
61 and older	79	15.8	89.7	5.1	5.1	12.8	50.0	26.9	10.3
Ethnic background:									
Black	237	47.7	75.4	16.1	8.5	22.6	48.5	24.7	4.3
White	176	35.4	81.7	6.9	11.4	16.0	49.7	21.7	12.6
Spanish-speaking	73	14.6	86.0	8.0	6.0	15.6	44.1	40.3	0
Other	12	2.4	...	...	...	...	...	...	...
Occupation:									
Blue collar	74	15.5	81.1	12.2	6.8	10.8	58.1	25.7	5.4
White collar	85	17.9	72.9	12.9	14.1	18.8	50.6	24.7	5.9
Professional	21	4.4	71.4	9.5	19.0	4.8	61.9	23.8	9.5
Student	39	8.2	61.5	28.2	10.3	20.5	43.6	35.9	0
Housewife	99	20.8	77.8	15.2	7.1	26.3	48.5	23.2	2.0
Retired, disabled, other	158	33.2	84.8	7.6	7.6	17.7	44.4	27.8	10.1
Chief complaint:									
Cardiorespiratory	52	10.7	86.5	11.5	1.9	23.1	44.2	28.8	3.8
Trauma	70	14.4	78.6	11.4	10.0	18.6	44.3	21.4	15.7
Eye, ear, nose, and throat	56	11.6	78.6	10.7	10.7	10.7	53.6	28.6	7.1
Neuropsychiatric	31	6.4	58.1	16.1	25.8	16.1	74.2	9.7	0
Gastrointestinal	50	10.3	80.0	12.0	8.0	14.0	54.0	28.0	4.0
Obstetrics and gynecology	62	12.8	65.0	26.6	8.5	32.3	43.5	19.3	4.8
Other	164	33.8	81.1	9.8	9.1	19.7	45.0	29.8	5.5

*Other characteristics (income, education, third-party payment scheme, number of visits to doctor each year, whether a private physician was the primary physician, patient's view of seriousness of illness, how patient selected clinic, whether patient had previously attended clinic) did not yield significant differences in attitudes toward women physicians.

†As compared to competence of male doctors.

age of black than white ($p<0.01$) or Spanish-speaking patients ($p<0.05$) preferred a female physician; 40 percent of Spanish-speaking patients said women physicians were less competent than men, compared with 25 percent of black and 22 percent of white patients ($p<0.02$).

When women patients were grouped simultaneously according to sex, age and ethnicity, ethnic differences became especially apparent (there were too few male patients in each age and ethnic category to allow statistical comparison). Almost one-third of black women under age 30 preferred a woman as their regular physician. In contrast, Spanish-speaking women under age 30 stood out in their *negative* attitude toward female doctors. The attitudes of white women less than age 30 fell midway between those of Spanish-speaking women and black women of the same age group. For example, among this age group, 54 percent of Spanish-speaking women, 32 percent of white women, and 20 percent of black women declared female doctors to be less competent than males ($p<0.01$).

"Blue-collar workers" were more likely than were those in other occupations to express negative attitudes toward female physicians. Responses of students presented an inconsistent pattern. Although higher percentages of students preferred a female doctor as their regular physician and a female doctor with whom to discuss personal problems, more students than other patients (including those under age 30) were inclined to declare female doctors less competent and less experienced than male doctors.

When patients were grouped according to their medical problem, certain clear-cut attitudinal trends were evident, the most striking being the relatively positive attitude of obstetrics and gynecology patients toward female physicians. Twenty-seven percent of these patients preferred a female doctor as their regular physician compared with 11 percent of other women ($p<0.001$), and 40

TABLE 2.—*Perceptions of Competence of Female Doctors Related to Perceptions of Experience, Friendliness, and Trustworthiness*

	*Experience**				*Friendliness**				*Trustworthiness**			
*Competetnce**	*N*†	*Percent More*	*Percent Same*	*Percent Less*	*N*†	*Percent More*	*Percent Same*	*Percent Less*	*N*†	*Percent More*	*Percent Same*	*Percent Less*
More	93	38	33	29	93	77	13	11	91	68	22	10
Same	233	7	71	22	228	32	55	13	233	19	75	7
Less	130	6	21	73	127	37	16	46	125	24	36	40

*Of female doctors compared to male doctors.
†Number of patients who responded to both questions.

TABLE 3.—*Interrelationship Among Biases of Patients Toward Female Doctors, Long-Haired Male Doctors, and Older Doctors*

	Experience of Long-Haired Male Doctors†				*Maximum Age for Doctors*		
*Experience of Female Doctors**	*N*‡	*Percent More*	*Percent Same*	*Percent Less*	*N*‡	*Percent Yes*	*Percent No*
More	60	30	17	53	63	53	47
Same	226	6	63	31	226	36	64
Less	170	7	26	67	179	36	64

*Compared with male doctors.
†Compared with other doctors.
‡Number of patients who responded to both questions.

TABLE 4.—*Biases of Patients Toward Female Physicians: Interrelationships with Bias Toward Older Doctors and Toward Long-Haired Male Doctors*

	*Competence of Female Doctors**				*Competence of Doctors over Age 50*†				*Competence of Male Doctors with Long Hair*†				*Prohibit Long Hair on Male Doctors*		
Female Doctors Limited to Certain Specialties	*N*‡	*Percent More*	*Percent Same*	*Percent Less*	*N*‡	*Percent More*	*Percent Same*	*Percent Less*	*N*‡	*Percent More*	*Percent Same*	*Percent Less*	*N*‡	*Percent Yes*	*Percent No*
Yes	51	25	14	61	52	87	6	7	48	8	21	71	51	92	8
No	404	22	55	23	398	61	25	14	397	14	59	27	413	48	52

*Compared with male doctors.
†Compared with other doctors.
‡Number of patients who responded to both questions.

percent were more inclined to confide their personal problems in female doctors compared with 22 percent of other women ($p<0.001$). Also, a higher proportion of this group (32 percent) than of other women (17 percent) judged female doctors to be more competent than male doctors ($p<0.001$).

Attitudes toward female physicians correlated with other attitudes

Patients who attributed one negative quality to female physicians were inclined to attribute other negative qualities to female physicians (Table 2). For example, patients who felt that female doctors were less competent than males also tended to declare them less experienced ($p<0.001$), less friendly ($p<0.001$), and less trustworthy ($p<0.001$) and were more likely than other patients to feel that female physicians should be limited to certain specialties ($p<0.001$). The converse was also true.

A very interesting relationship was found to exist between attitudes toward female doctors, toward male doctors with "long hair," and toward older doctors. For example, patients who gave female doctors unfavorable ratings on experience tended to give long-haired male doctors unfavorable ratings on experience ($p<0.001$), but the same patients were more inclined than other patients to reject the notion that there should be a "maximum age after which doctors must retire" ($p<0.001$) (Tables 3 and 4).

Relationships between experience with female physicians and attitudes toward the female physician

Toward the end of the interview, patients were asked if they had ever consulted a female physician. A majority (53 percent) had not. Of those who had, 49 percent said that they had a "good" experience, 19 percent a "bad" experience, and 32 percent neither good nor bad. More patients who

TABLE 5.—*Relationship of Contact with a Female Doctor to Attitudes Toward Female Doctors*

	Doctor Preference				Competence*					Experience*				
Seen by Female Doctor	*N*†	*Percent Male*	*Percent Female*	*Percent Either*	*N*†	*Percent More*	*Percent Same*	*Percent Less*	*Percent Don't Know*	*N*†	*Percent More*	*Percent Same*	*Percent Less*	*Percent Don't Know*
Yes	154	70	19	11	152	29	47	20	4	151	17	51	28	4
Good experience	75	64	26	10	72	32	50	13	5	70	26	46	24	4
Indifferent experience	47	74	14	12	44	22	53	22	2	44	6	69	25	0
Bad experience	30	84	6	10	29	30	30	33	7	29	10	37	43	10
No	174	83	10	8	170	16	47	25	12	170	11	46	36	8

*Of female doctors compared to male doctors.
†Number of patients who responded to both questions.

TABLE 6.—*Effect on Biases Toward Long-Haired Male Doctors and Older Doctors of Exposure to Female Doctors*

	Competence of Long-Haired Male Doctors*				Prohibit Long Hair on Male Doctors			Maximum Age for Doctors		
Seen by Female Doctor	*N*†	*Percent More*	*Percent Same*	*Percent Less*	*N*†	*Percent Yes*	*Percent No*	*N*†	*Percent Yes*	*Percent No*
Yes, good experience	70	11	63	26	76	52	48	75	47	53
Yes, indifferent experience	44	2	57	41	47	56	44	46	37	63
Yes, bad experience	29	13	35	52	28	75	25	29	24	76
No experience	170	11	61	28	171	54	46	176	40	60

*Compared with other doctors.
†Number of patients who responded to both questions.

had previously consulted female physicians were favorably inclined toward such doctors than patients who had never consulted one (Table 5). A higher percentage of these "exposed" patients preferred a female doctor as their regular physician ($p<0.001$) and preferred to consult a female physician about personal problems ($p<0.001$). They also gave female physicians higher ratings in competence (and trustworthiness) than did patients who had never consulted a female doctor ($p<0.001$).

The quality of experience as judged by the patients also correlated with patient attitude toward female physicians. Thus, many more favorable responses were received from patients who described their experiences with female doctors in favorable terms than were received from patients who described their experiences in unfavorable terms. Patients who complained of a bad experience with a female physician exhibited generalized negative attitudes toward women physicians and long-haired male doctors, and favorable attitudes toward older doctors (Table 6). The reverse was not true, however; patients with good experiences with female doctors were no more favorable in their attitudes toward long-haired doctors and no less favorably inclined toward older doctors than patients who had never consulted a female physician.

Discussion

A significant percentage of the patients interviewed had never consulted a female physician yet did not hesitate to offer negative opinions of female physicians. Thus, their attitudes constitute a generalized prejudice. Moreover, the prejudice against female physicians parallels several features of ethnic prejudice[2] in that prejudiced patients tended to have overgeneralized beliefs ("women doctors are inexperienced"), tended to believe that women physicians had many objectionable qualities, and tended to reject other "outgroup" doctors (for example, long-haired men).

Such prejudice may be reduced by contact between majority and minority groups in the pursuit of common goals.[2] Therefore, patient contact with female physicians with the goal of improved health may be expected to result in a reduction of prejudice. The current study provides suggestive evidence that this is the case.

A major determinant of prejudice against female professionals is the conflict which exists between society's ideal image of women and the image of the profession.[3,4] In American society, some of the preferred femininc attributes are personal warmth and empathy, sensitivity and emotionalism, compliance, dependence and deference, as well as absence of such "masculine" traits as aggressiveness, egotism, persistence, and

ambition.[4] By violating society's common image of femininity, the female doctor disconcerts both men and women. Thus, the attitudes expressed by a majority of patients are legitimized and endorsed by societal tradition.

"Machismo" may account for the high percentage of prejudiced responses by patients from Latin cultures.[5] Although bias was observed more frequently among Spanish-speaking patients than in any other group, these patients accounted for only 15 percent of the total sample; therefore, ethnic differences do not explain the high proportion of negative attitudes toward female doctors in the entire sample. The converse of the female role in traditional Puerto Rican culture is found in the "mother-centered"[6] families of many black Americans; this may help explain the comparatively positive attitudes of black women toward female physicians.

One very interesting exception to the prejudice against female physicians was the relatively positive attitude of the patients with obstetric or gynecologic complaints. This attitude is, on the one hand, a surprising result in that the specialty is not one of the few supposedly "compatible" with the female role,[4] nor has it attracted a particularly high number of women practitioners to its ranks.* On the other hand, the tradition of midwifery in Europe and in this country would support the notion of women in obstetrics and gynecology.

*In 1970, 7.1 percent of the total practicing obstetricians and gynecologists in this country were women. At that time women represented 20.8 percent of the total number of pediatricians, 14 percent of anesthesiologists, 18.6 percent of public health physicians, 12.7 percent of psychiatrists, 12.2 percent of pathologists, 5.7 percent of internists, 1 percent of general surgeons, and 6.9 percent of all physicians.[7]

The major limitation of the current study is the fault that besets all attitudinal surveys, namely, that what respondents say and what they do are not necessarily the same. The reactions of patients to their doctors are more accurately observed than predicted, and it is possible that one could design and carry out a controlled study to compare the reactions (for example, compliance with recommended treatment) of patients to male and female physicians. Clearly, the attitudinal trends observed in this study do not enable one to predict actual reactions of any one patient to a particular physician. Moreover, there are other variables in the physician-patient relationship,[8-11] and the patient presumably is reacting to their sum. What this study does accomplish is the systematic consideration of an heretofore little regarded variable—sex prejudice—in the doctor-patient relationship.

REFERENCES

1. Phelps CE: Women in American medicine. J Med Educ 43: 916-924, 1968

2. Allport GW: The Nature of Prejudice, Abridged Edition. Garden City, New York, Doubleday Anchor Books, 1958

3. Lopate C: Women in Medicine. Baltimore, Johns Hopkins Press, 1968

4. Epstein CF: Woman's Place: Options and Limits in Professional Careers. Berkeley, University of California Press, 1970

5. Hill R, Stycos JM, Back KW: The Family and Population Control: A Puerto Rican Experiment in Social Change. New Haven, College and University Press, 1959, p 58

6. Pettigrew TF: A Profile of the Negro American. Princeton, D Van Nostrand Company, Inc, 1964

7. Pennell MY, Renshaw JE: Distribution of women physicians, 1970. Woman Physician 27:197-203, 1972

8. Friedson E: Patients' Views of Medical Practice: A Study of Subscribers to a Prepaid Medical Plan in the Bronx. New York, Russell Sage Foundation, 1961

9. Bloom SW: The Doctor and His Patient: A Sociological Interpretation. New York, Russell Sage Foundation, 1963

10. Cartwright A: Patients and Their Doctors: A Study of General Practice. New York, Atherton Press, 1967

11. Korsch BM, Gozzi EK, Francis V: Gaps in doctor-patient communication—1. Doctor-patient interaction and patient satisfaction. Pediatrics 42:855-871, 1968

Refer to: Owsley JQ Jr: Camouflage and the augmentation mammaplasty. West J Med 120:101-104, Feb 1974

Augmentation mammaplasty has become a safe and accepted surgical procedure since the introduction of silicone prosthesis. Proper selection of the type and size of the implant and careful attention to making the line of incision as nearly invisible as possible are important for a natural-appearing breast. Placement of a silicone gel filled prosthetic implant through a periareolar incision achieves excellent contour and consistency in the augmented breast, with an essentially invisible scar.

Camouflage and the Augmentation Mammaplasty

JOHN Q. OWSLEY, JR., MD
San Francisco

THE IDEAL GOAL of a breast augmentation operation is to insert an adequate volume of inert augmenting material without leaving telltale signs of the surgical intervention. The first satisfactory augmenting material became available in the late 1950's, when medical grade silicones were introduced.[1]

For a time, injection of liquid silicone, a method of augmenting breast size without creating surgical scars, was greatly publicized in the popular news media. Unfortunately, significant complications occurred after these injections. Because the long term effects of injecting silicone fluid into the subcutaneous tissues have not been determined, the Federal Food and Drug Administration has ruled that liquid silicone should not be injected into the female breast. The only acceptable alternative breast augmentation requires a surgical incision so that a silicone prosthetic implant can be inserted into the retromammary space to provide the desirable volume and contour.

A silicone implant for this purpose designed by Cronin and developed by the Dow Corning Company in 1964 has proved to be a safe and cosmetically satisfactory prosthetic implant.[2] More than 50,000 pairs of these implants have been used,[3] which certainly suggests that women other than exotic dancers are requesting such operations. The most recent Congress of the American College of Surgeons in San Francisco had five exhibits devoted to augmentation mammaplasty, reflecting the increasing interest of surgeons in this operation.

What kind of women ask for augmentation mammaplasty? Early psychological studies of patients undergoing breast augmentation warned of possible problems in feminine identification and perhaps even more profound psychological disorders.[4,5] Although some of these women are indeed suffering from psychological disturbances, most of the patients who are requesting breast augmentation operations are well adjusted single or married women. The typical patient expresses anxiety and frustration about her lack of breast development and her disproportionately shaped body.

Consider, in this context, the tremendous psychological impact of the women's fashion industry. The latest Paris collections are quickly copied, mass produced and stocked by American department stores. Unfortunately, for the woman whose breasts are unusually small it is difficult to find

From the Department of Surgery, University of California, San Francisco.
Submitted March 22, 1973.
Reprint requests to: J. Q. Owsley, Jr., MD, 45 Castro Street, San Francisco, CA 94114.

Figure 1.—Appearance of typical patient requesting augmentation mammaplasty.

Figure 2.—Silicone implant has been placed through a periareolar incision. Removable suture aids in orientation of the placement.

the right size in ready-to-wear clothing. A dress that fits well around the hips is too loose around the bust. The frustration associated with finding a suitable fit often forces her into unfashionable styles, so that, for example, instead of a bikini the unhappy shopper is forced to settle for a less attractive one-piece bathing suit.

Plastic surgeons throughout the world have found that the augmentation mammaplasty operation gives generally good results.[6] Since the introduction of the Cronin prosthetic implants, numerous modifications have been made in the implant materials, including variations of the shape of the capsule and consistency of the contained silicone fluid.[7] Various types of inflatable implants enjoyed some popularity,[8] but they are less commonly used now because of late collapse of the implant that has been observed following leakage and absorption of the filling fluid. In some series three-fourths of patients who had such implants had complications of this kind.[9]

The submammary fold incision has been the customary surgical approach, but it leaves a visible scar which, no matter how fine, is a telltale clue to the operation and a source of concern to the patient. To minimize the scar, small and medium sized silicone filled implants have been placed through a submammary incision only four to five centimeters long. This is accomplished by gentle digital manipulation to gradually squeeze the implant through a keyhole opening into the prepared retromammary space. Patients are gratified to find that they have so small a scar.

An alternative periareolar incision is now proposed for insertion of the standard pre-filled silicone breast implant. A periareolar incision has long been the preferred approach for surgical correction of gynecomastia in males. Made, as it is, at the edge of the contrasting color between the pigmented areola and the surrounding skin, the junctional incision is difficult to detect when the scar has matured. This incision has been advocated for women also, but for the insertion of inflatable breast implants which can be easily introduced through the small opening in a collapsed state, and then filled in situ.[10] However, since inflatable implants are prone to complications, this surgical incision has not been widely used for augmentation mammaplasty. Insertion of the silicone-filled implant through an inconspicuous periareolar incision would appear to achieve our goal of camouflaging the site of incision.

The typical female areola varies in size but in its relaxed state it is seldom less than 3 centimeters in diameter. If a circumareolar incision is made around half the circumference of a 3-centimeter areola, the wound is a minimum of 4.5 centimeters long. Traction on this incision creates an access which has proved to be entirely adequate for placement of small to moderate sized implants. In almost all patients the smaller sized implants are preferred because of their more natural contour and consistency to palpation.

For many patients the operation can be performed under local anesthesia on an out-patient basis, although some prefer to be admitted to the

Figure 3.—Same patient as in Figure 1, two weeks after operation.

Figure 4.—Same patient three months after operation. Note inconspicuous scar formation.

hospital for operation under general anesthesia. Strict aseptic operating room technique is mandatory. When local anesthesia is used, standard preoperative medications are given. Supplementary intravenous diazepam (Valium®), given just before injection of the local anesthetic, may be useful in apprehensive patients.

When the patient is lying supine on the operating table, the existing breast tissue flattens out. What might appear to be a considerable depth of tissue between the skin and pectoralis muscle when the patient is standing is remarkably reduced. An inferior periareolar incision is made. The skin is undermined inferiorly for 3 or 4 cm, and then the incision is deepened through the breast tissue to identify the fascia overlying the pectoralis muscle. Electrocautery dissection reduces bleeding and helps to identify the tissue planes. The incision is deliberately angled slightly away from the areola to prevent undercutting the nipple and possibly injuring the larger glandular ducts. Dissection of the superior quadrants of the retromammary space is easily accomplished with a few sweeps of the finger in most cases. Below the level of the nipple a combination of sharp and blunt dissection is necessary to free the lower quadrants of the breast. Dissection of the lower retromammary space must be carried completely to the level of the submammary fold. Failure to dissect the lower section adequately can result in improper placement of the implant, which causes abnormal fullness of the superior portion of the breast.

Careful hemostasis is of utmost importance to prevent postoperative hematoma. A retractor with a fiberoptic light source attached is of great help in exploring the extreme recesses of the retromammary space to secure all bleeding vessels. Hematoma contributes to later formation of excessive fibrous tissue and scar contracture around the implant. This can cause undesirable firmness of the breast and may necessitate subsequent surgical revision. Therefore, detection of a significant hematoma in the early postoperative period has an important bearing on the final outcome of the operation. Immediate reexploration of the breast and evacuation of the hematoma may be indicated.

The periareolar incision has other advantages in addition to the improved cosmetic appearance of the scar. The incision is in a central relationship to all directions of the dissection, which improves visibility and facilitates hemostasis. At this level there is less difficulty in identifying the proper plane of dissection along the fascia overlying the pectoralis muscle. When a submammary incision is used, the lower border of the muscle is not always readily identified, which may result in an unnecessarily bloody dissection in or under the muscle. Finally, less stress is exerted upon the periareolar incision than is placed on the inferiorly located submammary wound which carries the maximum weight of the prosthetic implant as the patient resumes erect activity during healing.

I now prefer to use the silicone implants manufactured by the Heyer-Schulte Corporation. They are thin, soft silicone rubber bags which contain the fluid silicone material. The implants are not backed with dacron patches, and do not attach to the chest wall. With an implant of this kind the consistency and appearance of the breast are more natural. The implant is introduced through the incision by manipulation of the fingers while the

wound edges are held apart by standard flat-blade retractors. This maneuver requires patience and gentleness as the bag is manipulated little by little into the cavity and the fluid contents are squeezed inside. On the posterior aspect of the implant there is a loop through which a heavy silk suture can be temporarily passed to aid in orientation of the position of the implant. The final placement of the implant is subsequently maintained in the breast by the surrounding thin fibrous capsule which forms within a few weeks after operation.

The satisfactory contour and near-normal consistency of the augmented breasts are achieved by careful selection of implants of appropriate size. If the implant fits the pocket satisfactorily, no additional fixation is necessary. No local medications are instilled into the cavity nor is any drainage mechanism introduced. Drainage is no substitute for thorough hemostasis. With care taken to assure accurate approximation of the edges of the incision, the breast tissue is sutured in two layers with absorbable sutures. The subcuticular approximation of the skin is followed by a fine running suture of nylon in the epidermis. A supportive dressing is maintained for at least 14 days following operation. Movements of the patients' arms are restricted for two weeks and physical activities, such as tennis and swimming, are prohibited for at least six weeks.

In its retromammary position the silicone implant is soon surrounded by a capsule of smooth, thin, fibrous tissue. In an occasional patient, the scar capsule thickens and contracts, causing excessive firmness of the breast. Hematoma is most likely a contributing cause in this reaction, although it has been speculated that the presence of Dacron fixation patches on the implant may provoke excessive fibrotic reaction in the capsule.[9] While it is difficult to prove this relationship, clinical experience has suggested less frequent occurrence of late capsular contracture when implants not having Dacron backing are used. Cases of capsular contracture are treated by secondary capsulectomy and replacement with implants that are not backed with that material.

Infection, while always a possibility, has been rarely encountered. I have not had occasion to remove a breast implant because of wound infection. Clinical symptoms related to so-called allergic or foreign body reaction to the silicone implants have not been observed.

Since the breast tissue overlies the implant, it is readily available for clinical examination. Cystic masses in the breast tissue have occasionally been observed, and usually have subsided spontaneously, although excisional biopsy of a persistent cystic mass was done in one case. Although a few cases have been reported, I personally have not seen a patient with breast carcinoma occurring after an augmentation mammaplastry.

Patient satisfaction is gratifyingly high after the operation. Although the surgeon may occasionally observe that the breasts are firmer than is ideally desirable, patients rarely express dissatisfaction and are usually delighted with the appearance and contour. Transient alteration in nipple sensation is common following either the submammary or periareolar incisions, though sensitivity and erectile function generally return to normal within a few months. Only one patient in 15 years said she believed she had permanent diminution in nipple sensation, though the nipple is sensitive to pinprick and shows normal erectile properties. In her case the augmentation was done through a submammary incision.

REFERENCES

1. Marzoni FA, Upchurch SE, Lambert CJ: An experimental study of silicone as a soft tissue substitute. Plastic and Reconstructive Surgery, 24:600-608, 1959

2. Cronin TD, Gerow FJ: Augmentation mammaplasty—A new natural feel prosthesis, *In* Transactions of the Third International Congress of Plastic Surgery, Excerpta Medica Foundation, Amsterdam, 1964, pp 41-49

3. Dow Corning: Advertisement. Plast Reconstr Surg 48, 1971

4. Edgerton MT, McClary AF: Augmentation mammaplasty, with special reference to use of the polyvinyl alcohol sponge. Plast Reconstr Surg 21:279-305, 1958

5. Edgerton MD, Meyer E, Jacobson WE: Augmentation mammaplasty—II. Further surgical and psychiatric evaluation. Plast Reconstr Surg 27:279-302, 1961

6. Hoopes JE, Edgerton MT, Shelley W: Organic synthetics for augmentation mammaplasty—The relation to breast cancer. Plast Reconstr Surg 39:263-269, 1967

7. Cronin TD, Greenberg RL: Our experience with the silastic gel breast prosthesis. Plast Reconstr Surg 46:1-7, 1970

8. Tabari KK: Augmentation mammaplasty with simaplast implant. Plast Reconstr Surg 44:468-476, 1969

9. Williams JE: Experiences with a large series of breast implants. Plast Reconstr Surg 48:233-257, 1972

10. Jenny H: Advertising brochure of the Heyer-Schulte Company.

Refer to: Greenberg LM, McMahon SA, Deem MA: Side effects of dextroamphetamine therapy of hyperactive children. West J Med 120:105-109, Feb 1974

Side Effects of Dextroamphetamine Therapy of Hyperactive Children

LAWRENCE M. GREENBERG, MD, *Davis, California*
SHIRLEY A. McMAHON, MD, *Marblehead, Massachusetts*
MICHAEL A. DEEM, PhD, *Washington, D.C.*

Dextroamphetamine, prescribed in the treatment of hyperactive children, was associated with significant personality deterioration in five of 26 treated cases. Discontinuance of the drug and, in some cases, substitution of others was followed by lessened symptoms of disorganization or of toxicity. In general, children being treated with psychostimulants should be kept under careful observation for untoward reactions.

DEXTROAMPHETAMINE in the treatment of hyperactivity has become increasingly widely used since its introduction in the 1930's.[1] For a time use of the drug for this purpose received little criticism because the side effects—for example, anorexia and insomnia—were generally thought to be relatively benign and usually transient. Recently, a limited number of cases of drug-associated psychosis or severe personality deterioration have been reported in children.[2-4] On the basis of our own experience, we believe these phenomena are not so rare as was previously thought. It is the purpose of this paper to report five cases of significant personality deterioration among 26 school-age hyperactive boys treated with dextroamphetamine at Children's Hospital of the District of Columbia. The children were subjects in a double blind, placebo-controlled, short-term comparative study of the effects of dextroamphetamine and two other medications on hyperactivity and associated behaviors. The dosage schedule of dextroamphetamine was prearranged but subject to reduction or termination when side effects were encountered. Medication was begun with 5 mg in the mornings and increased 5 mg every three days to a maximum level of 20 mg morning and afternoon.

Reports of Cases

CASE 1. The patient, seven years of age, was referred because of nervousness, decreased attention span, and increased activity at school. His mother complained of his lying, crying, temper tantrums, low frustration tolerance, overly dependent, clinging behavior, enuresis (twice a week), and running away from home. He was the third of seven children in an intact family living in a one-bedroom apartment and was clearly labeled by his father as "retarded" and his school papers characterized as "junk." His mother, the

This work was supported in part by the USPH grant MH 15134 from the National Institute of Mental Health. Dr. Greenberg is Associate Professor of Psychiatry and Pediatrics, University of California, Davis, School of Medicine. Dr. McMahon is in pediatric practice in Marblehead, Massachusetts and Dr. Deem is Research Associate, Children's Hospital, Washington, D.C.

Submitted December 1, 1972.

Reprint requests to: L. M. Greenberg, MD, Department of Psychiatry, University of California, Davis, School of Medicine, Davis, CA 95616.

primary caretaker, appeared to be a concerned, warm woman who was overly burdened with children and financial problems. His father, working two jobs from 6 a.m. to 9 p.m. but earning only $100 a week, was a rejecting, rather punitive man who could not tolerate the boy's crying and babyish behavior. There was a history of prematurity followed by normal developmental landmarks. A history of pica and four to five frontal headaches a month were also reported.

The patient presented as a friendly child who had difficulty understanding simple instructions. Physical findings included profound myopia, flat feet, an incurved fifth finger, equivocal plantar reflex on the right side, posturing on heel gait, and failure to perform tandem gait. The WISC full scale IQ was 63, with verbal IQ of 74 and a performance IQ of 58. The Rorschach protocol was interpreted as primitive and immature. The psychiatrist described the boy's thinking as primitive and perseverative. The patient claimed to be only five years of age and was primarily concerned that his favorite truck would be stolen by his only friend. He was classified as having a chronic brain syndrome and "healthy response." (The diagnostic classification proposed by the Group for the Advancement of Psychiatry[5] was utilized during this study.)

During the course of treatment with dextroamphetamine, the pediatrician reported observations of a transient increase in blood pressure and heart rate, as well as mild anorexia, headache, and drowsiness. At the conclusion of the eight-week treatment period, the pediatrician observed bizarre, inappropriate behavior (that is, talking to himself) on a dosage of 15 mg twice a day. There were no appreciable changes noted in school or home performance and behavior, although the patient was reportedly "quieter" and "less nervous" after taking the medication. There were a number of significant environmental changes (moving to a new home with more adequate space, starting in a new classroom with a new teacher, replacement of glasses and being injured in a fight with another youngster), but none of these changes were judged to account for the observed inappropriate behavior. WISC performance scores were noted to have improved; however, verbal responses were noted to be more perseverative. Rorschach content was judged to be bizarre and consistent with a diagnosis of borderline psychosis. The psychiatrist reported clinical deterioration, with borderline thought processes and fantasies more in evidence. The patient claimed to be five years old but would "turn 13" at his next birthday. He appeared very slow and lethargic. He spoke of wanting to displace his youngest sister in the mother's bed and of feeling "sad" all of the time. He was fearful of monsters in his dreams and reacted to the play puppets as though they were monsters. The initial diagnostic impression was changed to developmental deviation (severe), a category which was considered equivalent to borderline psychosis. With the discontinuation of medication, symptoms of disorganization became less prominent.

CASE 2. A seven-year-old boy was referred with complaints about his school behavior: He did not sit still, did not pay attention, left the classroom, and was quite disruptive. Similar behavior was described at home. In addition, a severe speech defect, which may have contributed to his being the scapegoat of the classroom, was reported. He lived with his two working parents and two-and-one-half-year-old adopted sister in a large, comfortable house. There had been a succession of babysitters and caretakers since the patient's birth. The parents had been actively seeking medical attention for him for some time and were very concerned but perhaps overly indulgent and permissive while at the same time considering "putting him away."

On review of the history it was learned that biparietal depressions of the skull had been observed by the mother at the time of birth and she also reported a neonatal feeding problem. Developmental milestones had been delayed, with walking at 18 months and speaking at two and one-half years. The patient was said to have become hyperactive at two years with no known precipitating factors.

On physical examination, right parietal depression, abnormal speech, flat feet, posturing on heel and toe gaits, and dysdiadochokinesis were noted. WISC scores were: Full scale IQ 69, verbal IQ 63, and performance IQ 82. The patient was described by the psychologist as hyperactive, impulsive, irritable and depressed. The psychiatrist noted that he was poorly related, somewhat negativistic, and fearful. Eating was a frequently mentioned concern, and his human drawing was quite primitive, the figure having dark eyes and an enormous mouth. Two diagnoses were given: (1) chronic brain syndrome, (2) neurotic disorder, marked by negativism and passive-aggressive behavior.

After eight weeks of treatment, reports from

home and school noted little change in behavior. There were no known significant environmental changes although parental concern and anger were more clearly evident. The pediatrician had noted increased heart rate, blood pressure, sweaty palms, decreased appetite and weight on a dose of 20 mg a day, and the dose then was lowered to 15 mg a day. On the final examination the patient was described as more depressed, more perseverative, and with some question of disorganization of thought processes. Both the psychologist and psychiatrist reported increased depression, with anger, withdrawal, and pronounced negativism. The psychiatrist's diagnosis was changed to one of possible character disorder. The symptoms of toxicity abated with cessation of medication.

CASE 3. A nine-year-old patient was referred from the psychiatric outpatient service with a history of hyperactivity, fighting, lying, stuttering, and nail biting. Hyperactivity was said to begin at the time he began walking. The child had been enuretic until age eight. Living with his two working parents, he shared a bedroom with his only sibling, a four-year-old girl, although he had his own room. His mother appeared to be less involved with the boy than was his father, who tutored him every evening in a basement room converted into a classroom. The mother had had excessive weight gain and gestational diabetes during pregnancy. The infant required oxygen at birth and remained in an incubator for the first 24 hours. He was a slow feeder and had frequent colic. Physical findings included one incurved fifth finger, posturing on all gaits, synkinesis, awkwardness in fine and gross motor coordination, dysdiadochokinesis, and dysrhythmia on tapping. WISC scores were: Full scale IQ 87, verbal IQ 90, and performance IQ 86. The Rorschach responses indicated a great deal of anxiety and poor impulse control. In the psychiatric interview the patient appeared immature, restless, irritable, negativistic, and excessively dependent. Concern with getting enough food was frequently verbalized. He was mildly depressed and moderately anxious. The diagnosis was chronic brain syndrome and reactive disorder, marked by chronic anxiety.

Following the treatment period, attention span and work capacity were considerably improved and he was less distractible. No significant environmental changes were noted. During the course of medication, he experienced some sleepiness and loss of appetite which subsided when the dose of dextroamphetamine was reduced to 10 mg twice a day. The pediatrician noted that he seemed to be more dependent and clinging. The Rorschach seemed qualitatively worse to a slight degree. In the psychiatric interview, the patient seemed better related and less depressed. However, a "manic-like" quality with some perserveration and disorganization of thought processes were noted. The diagnosis was unchanged.

On reduction of the dose to 5 mg twice a day side effects abated and some reduction in hyperactivity was maintained.

CASE 4. A nine-year-old boy was brought to the center because of fighting, difficulty with school routines, and hyperactivity in school. He was the oldest of three boys living with his working parents in adequate housing. Since his mother worked days and his father evenings, one parent was always available as caretaker. His mother tended to blame the school for the boy's problems and seemed somewhat uninvolved and unconcerned about him, but his father was concerned with his provocative and "immature" behavior in the home.

The medical history was unremarkable. The pediatric examination was normal except for clumsiness and dysdiadochokinesis. The patient's behavior was seen as aggressive and rude during the examination. The WISC full scale IQ was 85, and other psychological measurements were average. On psychiatric interview, the child was described as appealing, warm, well-related, although hyperactive and admittedly "nervous." It was felt that emotional disturbance was absent to mild, and the diagnosis of developmental deviation (mild) was assigned. This category might be considered equivalent to that of "minimal brain dysfunction" in other nomenclatures.

During the eight-week course of dextroamphetamine therapy, definite side effects were noted. By the end of the first week, the patient was more grouchy. On a dose of 20 mg twice a day, at the four-week visit the patient had increased blood pressure and heart rate, sleeplessness, and decreased appetite and weight. The child acted angry and said that he thought the medicine was "poison." Two weeks after the dose was decreased to 15 mg twice a day, the boy no longer complained and showed no signs of these particular side effects. However, he remained hyperactive and became increasingly negativistic and provocative. On the same dose at the eighth week, he was angry, babyish, made animal noises, and crawled into the bottom of a toy closet to disrobe. In the

psychological examination, he showed improvement in performance scores, but throughout the examination he made many stereotyped gestures and grimaces. The Rorschach protocol revealed many pathological signs including gross disorganization and mistakes in color naming. He demonstrated primitive, bizarre responses, touching and smelling the cards. Indeed, at times he attributed specific smells to particular cards or parts of cards and was very suspicious of the procedures. The psychiatric evaluation showed clear-cut deterioration with severe impulsiveness and feelings of helplessness, of being "bad," and of being picked on by others. There was evidence for more primitive thinking and inability to contain fantasies. However, as with performance tests, school grades had improved during dextroamphetamine therapy.

After the medication was discontinued, many of the symptoms subsided. A course of thioridazine (Mellaril®) was begun, with some improvement in relatedness and a decrease in hyperactivity. After a short time, increased appetite and excessive weight gain were observed. Finally methylphenidate (Ritalin®) was prescribed, with little improvement in hyperactivity. Referral for psychotherapy had been made at the end of the dextroamphetamine trial, but the family was unable to carry out the recommendation successfully.

Case 5. The patient, aged six, was referred because of his behavior both at home and at school. His mother felt he was bored, did not concentrate, and was overactive. He cried easily and slept fitfully. He had been hyperactive since infancy. He lived with his mother, who worked since his birth, and a two-year-old sister with whom he shared a bedroom. His father had separated from the family six months before the evaluation but visited frequently and without conflict. Although the babysitter, the same one since the patient's birth, was described as "strict," the parents appeared to be too permissive and indulgent. The medical history was unremarkable, except for weekly frontal headaches and frequent nose bleeds. On examination, the child was perceived as immature, distractible, and distant. He had flat feet and a high arched palate. There was some clumsiness, and balance was only fair. He was also noted by the psychologist to be poorly related. The WISC full scale IQ was 102, with a verbal IQ of 116 and a performance IQ of 86. There were great difficulties with visual-motor skills. The psychiatrist found the patient to be only moderately well related, with poor eye contact. His thoughts were perseverative, and there were a number of hostile fantasies which were poorly controlled and led to a disruption of speech. He manifested numerous eye tics, gestures, and mannerisms when under stress and spontaneously wished to be made of metal so he would be safe if shot. He frequently knocked his head when his "brain was not thinking right." He described having thoughts that he could not "get out of his head." The diagnoses of chronic brain syndrome and reactive disorder were made although his behavior sounded borderline at times.

During treatment with dextroamphetamine, many side effects were noted, including irritability, crying, sleeplessness, dizziness, and decreased weight and appetite. The dose was never higher than 10 mg twice a day, and the physical side effects lasted only briefly. However, by eight weeks, the child appeared depressed to the pediatrician. A significant environmental change was noted: In the sixth week of treatment he moved to the father's apartment and a new school where discipline was "stricter." Behavior was reported to have become better in the home but unchanged in the classroom after the fourth week of medication. While improvement occurred on performance tasks in the psychological battery, deterioration was evident in the Rorschach responses. The child became overreactive, expansive, and very poorly controlled. The psychiatrist found him very confused, distractible, depressed, and preoccupied with aggressive fantasies. He was giggly, labile, inappropriate, and poorly related. He occasionally expressed much anger and spoke of "something wrong with my brain" and a memory problem. He was diagnosed as being borderline psychotic.

The dextroamphetamine was discontinued and chlorpromazine (Thorazine®) was given. This change was followed by improvement in behavior, integration of thought processes, and the expression of more appropriate affect.

Discussion

These cases have been presented to alert the clinician to the need for caution in prescribing the psychostimulant, dextroamphetamine, in the treatment of hyperactive children. We have been impressed with the profound influence upon personality organization which this agent may exert during treatment for hyperactivity. Since many children who are perceived as hyperactive have

emotional disorders, either of a primary or secondary order, it is necessary to be quite careful in making observations about changes in behavior, both desirable and undesirable. Extreme care should be taken to assess the underlying personality organization of patients before administering the drug, and to continue frequent reassessment of those children in whom integration of personality seems tenuous. It should be noted that other psychostimulants—for example, Ritalin—have also been implicated in causing such disturbances.[4] In our clinical experience, these severe side effects appear to have occurred with much less frequency with methylphenidate than with dextroamphetamine. However, this is only a clinical impression which has not been carefully documented.

The cause for this disorganizing influence in some patients is not clear. However, recent studies have suggested that hyperactive children may vary in their baseline level of autonomic nervous system function, and it is conceivable that further disorganization of thought processes takes place. Additional research is needed to establish the presence of such a relationship between clinical behavior and autonomic function.

REFERENCES

1. Greenberg L, Lipman R: Pharmacotherapy of hyperactive children—Current treatment practices. Clin Proc Child Hosp (DC) 27:101-105, Apr 1971

2. Lucas A, Weiss M: Methylphenidate hallucinosis. JAMA 217:1079-1081, Aug 1971

3. Ney P: Psychosis in a child associated with amphetamine administration. Canad Med Assoc J 97:1026-1029, Oct 1967

4. Weiss G, Minde K, Douglas V, et al: Comparison of the effects of chlorpromazine, dextroamphetamine, and methylphenidate on the behavior and intellectual functioning of hyperactive children. Canad Med Assoc J 104:20-25, Jan 1971

5. Psychopathological disorders in childhood—Theoretical considerations and a proposed classification. Group for the Advancement of Psychiatry, 1966

6. Satterfield J, Cartwell D, Lesser L, et al: Physiological studies of the hyperkinetic child. Am J Psychiat 128:1419-1424, May 1972

Management of Essential Tremor

I believe that the differential diagnosis of essential tremor versus parkinsonism is one that every practicing internist has probably fairly frequently faced in his practice, particularly if he has middle-aged or elderly people, as most of us do. Everyone, I think, recognizes the parkinsonian tremor and almost invariably recognizes it correctly . . . I'd like you to emphasize in your analysis of the parkinsonian patient, not so much the tremor (which is the obvious thing that grandmother recognizes and the next-door-neighbor knows what's wrong with the patient as soon as you do) but to emphasize something that in its early manifestations is more subtle, and yet, in terms of therapy, much more important . . . and that is the rigidity and slowness of muscle movement that is the earliest manifestation almost invariably of parkinsonism. This often antedates the occurrence of tremor and sometimes is far more profound, in fact, than the tremor, although the reverse also may occur. This is important because, in its early manifestations, although relatively easy to diagnose if you think to look for it, it is usually easy to miss if you don't have it in mind. And the reason that this is important from the standpoint of essential tremor is that it is the single most important distinguishing factor between the disorder "essential tremor" and the disorder "parkinsonism"; and both have absolutely different therapeutic implications.

—Oscar M. Reinmuth, MD, *Miami*

Extracted from *Audio-Digest Internal Medicine*, Vol 20, No. 14, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Refer to: Holt SA, Friedland GW: Neonatal necrotizing enterocolitis—Clinical and radiological features. West J Med 120:110-115, Feb 1974

Neonatal Necrotizing Enterocolitis

Clinical and Radiological Features

STEVE A. HOLT, MD, and GERALD W. FRIEDLAND, MD, *Stanford*

NECROTIZING ENTEROCOLITIS is an often fatal inflammatory disease involving the intestinal tract of premature infants in which intestinal perforation is common. The condition may mimic obstruction both clinically and radiologically. Cases believed to represent this entity have been diagnosed diversely as neonatal appendicitis, peritonitis, colitis, ileitis, functional ileus, spontaneous ileal perforation, pneumatosis intestinale and portal vein gas.

This paper describes a retrospective study which was designed to analyze the clinical and radiological findings, therapy and prognosis in ten proven cases of neonatal necrotizing enterocolitis diagnosed over a three-year period. A further purpose of the study was to compare the contribution of the clinical history and physical findings with the role of radiology in making the diagnosis. An important question considered was whether the plain films of the abdomen would suffice in making the radiological diagnosis, or whether barium contrast studies of the small bowel and colon provided sufficient additional information to warrant their use in all ill premature infants. A misleading finding in the barium contrast study of the small bowel, not previously reported, will be described.

From the Department of Radiology, Division of Diagnostic Radiology, Stanford University School of Medicine.

Supported in part by grant RR-81 from the General Clinical Research Centers Program of the Divisions of Research Sources, National Institutes of Health.

Submitted January 18, 1973.

Reprint requests to: G. W. Friedland, MD, Department of Radiology, Division of Diagnostic Radiology, Stanford University School of Medicine, Stanford, CA 94305.

Patients Studied

The radiographs and medical records were reviewed on all patients who had a surgical or pathological diagnosis of necrotizing enterocolitis during 1967-1970. Necrotizing enterocolitis was diagnosed in ten patients out of 2,492 admitted to the Sick Infant and Premature nurseries. Of the ten, five were born at Stanford Medical Center and five were transferred from other hospitals within the area.

Clinical Findings

Prenatal History

Only three of the mothers had no prenatal complications. Two mothers leaked amniotic fluid before delivery. Two others had vaginal bleeding during pregnancy and one of them received no prenatal care. One mother had placenta praevia. At delivery the amniotic fluid of one mother

Necrotizing enterocolitis is an uncommon but dangerous disease in premature infants. Ten cases, seen over a three-year period at the Stanford University Medical Center, represented an incidence of 0.4 percent. The patients, six of whom died, derived from a general population, in contrast to the large series of patients reported in the literature in which the incidence was from 0.9 percent to 3.7 percent.[3-6]

The initial symptoms—rapid respiration, periodic breathing, lethargy and irritability—were identical to those which occurred in numerous infants who had respiratory disease. Subsequent symptoms (abdominal distension, in 100 percent; vomiting, 80 percent; apneic spells, 70 percent; jaundice, 70 percent; guaic-positive stools, 60 percent) were those of nonspecific acute abdominal disease.

The radiologist first made the diagnosis in 90 percent of cases. Interstitial air in the wall of the gut and the retroperitoneum, and portal vein gas were the most diagnostic radiographic features. Barium contrast studies were not helpful, and in one case led to the erroneous diagnosis of small bowel volvulus.

Plain abdominal radiographs must be taken of all premature infants with symptoms of nonspecific acute abdominal disease. If the radiographs are negative, but symptoms continue, they should be repeated at frequent intervals, for early diagnosis is critical to institution of proper therapy.

smelled foul; in another mother fever developed during an unsuccessful trial of labor that was terminated by cesarean section. Psychiatric problems requiring treatment with phenothiazines and other medications complicated one pregnancy.

Two babies were born by frank breech delivery and one by cesarean section. One was born in an automobile in the hospital parking lot.

Neonatal History

This series comprises six boys and four girls and includes four sets of twins. Only one twin in each pair contracted the disease. The mean birthweight of the affected infants was 1,576 grams with a standard deviation of 175 grams. Birthweight of the smallest infant was 1,050 grams while the heaviest infant weighed 2,409 grams. Only four patients weighed more than 1,600 grams. The mean gestational age was 32 weeks and the range was 28 to 38 weeks.

Neonatal problems other than prematurity occurred in all infants. All presented with respiratory problems including transient respiratory difficulty in two, periodic apneic pauses in one, aspiration pneumonia in two and respiratory distress syndrome in four. Cardiac catheterization demonstrated hypoplasia of the left heart with coarctation of the aorta distal to a patent ductus arteriosus in one patient who was symptomatic from birth with congestive heart failure.

Hyperbilirubinemia occurred in seven infants, two of whom required exchange transfusion. Some degree of acidosis, requiring correction, existed in most infants. In one baby omphalitis developed before onset of clinical symptoms. An umbilical vein catheter was introduced in two infants while seven received umbilical artery catheters.

Symptoms

Most infants had rapid respirations (greater than 60 to 70 breaths per minute), periodic breathing, lethargy and irritability before the onset of abdominal symptoms. These nonspecific symptoms also occurred in numerous infants who had respiratory disease and who did not subsequently have necrotizing enterocolitis. Symptoms suggesting abdominal disease appeared in six infants between the third and seventh day of life. Two infants were symptomatic on transfer to Stanford Medical Center from other hospitals on the eleventh and fifteenth days of life. Abdominal distension was observed in all infants as one of the earliest features. Vomiting and regurgitation occurred in eight infants; this phenomenon pre-

Figure 1.—Upright film of the abdomen showing gaseous distension of the bowel with multiple air fluid levels.

ceded abdominal distension by one day in two cases. Apneic episodes occurred in seven infants and seven appeared clinically jaundiced. Six babies passed guaic-positive stools.

Radiographic Features

Plain Film Features

Increased intraluminal gas and fluid were seen in all patients early in the course of the disease (Figure 1). Waxing and waning bouts of bowel distension occurred in two patients before the development of other more specific radiographic features at one month of age. In all ten patients there was a "bubbly" pattern which was sometimes localized to the right lower quadrant but frequently was more extensive and reflected the extent of the disease (Figure 2). Intramural gas occurred in nine patients (Figure 3). Hepatic portal venous gas was seen in eight (Figure 4); in one, it cleared over a period of several hours. Free intraperitoneal air was demonstrated in three patients (Figure 5).

Contrast Studies

Gastrointestinal contrast studies were performed on three patients. In one baby, the small bowel series was misleading and incorrectly suggested volvulus (Figure 6). Barium studies of the small bowel, performed through the gastrostomy tube in one of the patients, demonstrated segmental dilatation, narrowed segments, thickened folds and an irregular mucosal pattern. A barium enema study appeared normal in a third patient.

Figure 2.—Left flank with the patient supine showing a "bubbly" or "frothy" appearance to the bowel and curvilinear shadows indicating intramural gas.

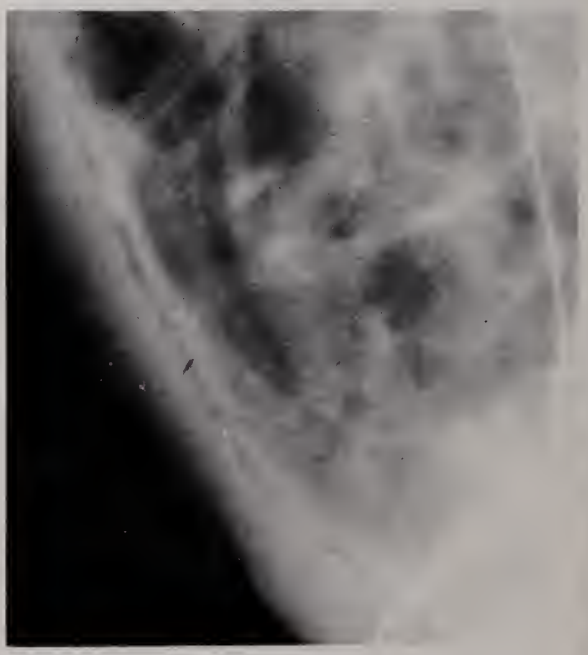


Figure 3.—Right flank with the patient supine showing streaks of intramural air in the cecum and ascending colon, and a thick linear streak of air in the properitoneal fat stripe.

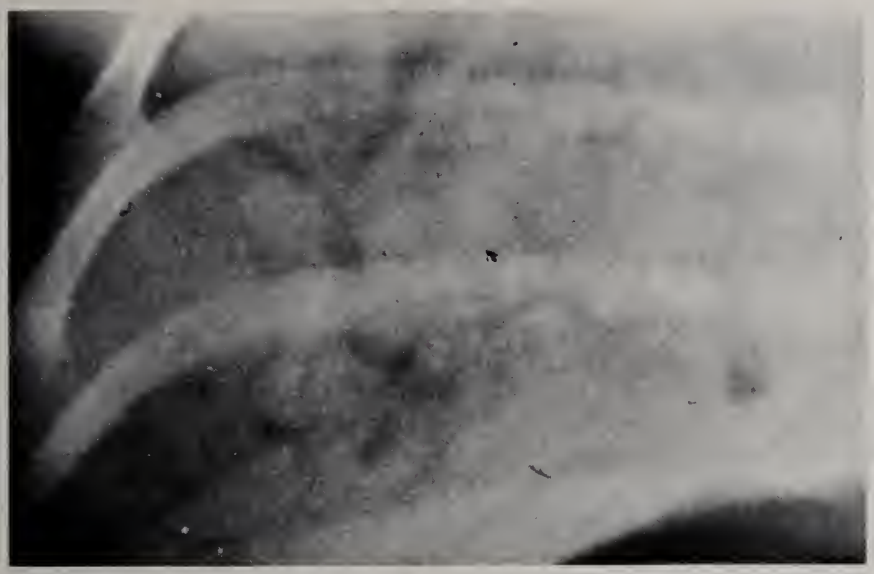


Figure 4.—Liver, showing the typical appearance of gas in the portal venous system.

Figure 5.—Domes of the diaphragm with the patient supine and the film exposed using a horizonal beam. A large pneumoperitoneum is present (closed arrows). Fluid levels are present in the gut. A faint shadow of gas in the portal venous system can be seen (open arrow).

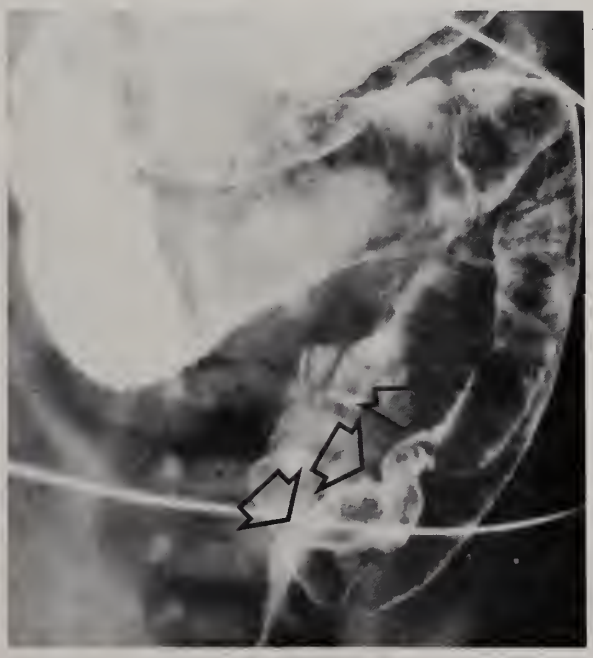


Figure 6.—Small bowel series. The upper jejunum is dilated. Barium did not pass beyond the upper quarter of the jejunum. At the site of obstruction the gut has a helical appearance (open arrows) suggesting a volvulus along the longitudinal axis. Gas is visible in gut distal to the obstruction. At operation extensive necrotizing enterocolitis was present but no volvulus was found.

Treatment

Nine patients were treated surgically. The other, who had congenital heart disease, was treated medically. Medical management consisted of bowel decompression, appropriate broad spectrum antibiotic therapy, respiratory assistance, maintenance of electrolytes, fluids and acid base balance, and maintenance of a constant body temperature. The surgical procedures varied and were primarily determined by the patient's condition and the pathologic situation encountered.

Pathology

Pathological findings varied, reflecting the extent and severity of the disease. Short segments of small bowel or cecum were affected in four patients but in the majority the disease involved one-half to one-third of the small bowel. The bowel appeared gangrenous from the ligament of Treitz to the distal transverse colon in one patient. Commonly, involved segments appeared dilated.

Decidedly thinned bowel wall was noted in some areas; the latter appeared hemorrhagic and bluish-gray in color. Furthermore, pneumatosis intestinale, mucosal ulcerations, fibrinous exudates, pseudomembrane formation and acute and chronic inflammation and vascular engorgement were present. The necrotic areas of bowel were clearly demarcated, and the tissue changes progressed in a manner similar to those of other ischemic diseases, suggesting that they were caused by mesenteric vasoconstriction. Portal vein gas and areas of perforation were found in some patients. Viewed microscopically, the bowel revealed hemorrhages into mucosa, lamina propria and serosa, infiltration of the interstititium by mononuclear cells, sloughing and ulceration of the surface epithelium, and areas of deep ulceration and perforation.

Bacterial Cultures

Blood or peritoneal cultures were positive in five patients. The gastric content, intestinal content or stool was positive in four. Organisms cultured were E. coli and the Klebsiella aerobacter group. In two patients, all cultures were sterile.

Prognosis

Six infants died, accounting for 5 percent of deaths from all causes in our nurseries during this period. A single patient, treated medically, died but, because of the underlying heart disease, may not have survived regardless of the treatment employed. The three survivors were treated surgically.

Birthweight seemed to be a significant factor influencing survival: two of the three patients who survived weighed more than 1,500 grams at birth. Although positive blood cultures and hepatic portal venous gas usually portend death, blood and peritoneal cultures were positive in one survivor, while hepatic portal venous gas existed in two survivors. On the other hand no infants survived who had pneumoperitoneum.

All survivors are still living, and have been followed for periods of from two to 29 months. None are entirely normal. Two patients, who are gaining weight, have suffered from respiratory tract infections while one patient has iron deficiency anemia. One baby was readmitted to the hospital because of failure to thrive, the cause of which has not been discovered.

Discussion

In nine of the ten cases in this series, the radiologist first made the correct diagnosis. In two cases, the diagnosis was made from a chest radiograph. Clinical signs were those of nonspecific acute abdominal disease and usually appeared between the third and seventh day of life; the most common were vomiting, abdominal distension, apnea, jaundice and gastro-intestinal bleeding.

Recognition of the earliest radiological features is critical to the institution of proper therapy. Premature infants who have bowel dilatation or signs of obstruction must be particularly suspect (Figure 1) and further films should be obtained.

We have found plain film features to be the most useful for diagnosis and for following the course of the disease (Figures 2, 3, 4, 5). Common radiographic features in our series included increased intraluminal gas and fluid (Figure 1), a "bubbly" or "frothy" appearance to the bowel (Figure 2), intramural gas (Figures 2 and 3), hepatic portal venous gas (Figure 4) and pneumoperitoneum (Figure 5). We are uncertain whether the "bubbly" or "frothy" appearance so charactertistic of this condition delineates only intramural gas or whether it represents a combination of intramural gas with mixed gas and blood in the bowel lumen. Contrast studies, performed in three infants, were of no value. In one case, the findings on a small bowel series were positively misleading (Figure 6). The value of barium enemas to exclude mechanical obstruction or agang-

lionosis must be weighed against the potential hazard of perforation and extravasation of contrast medium into the peritoneum. Critically ill premature infants may be unable to tolerate contrast examinations.

In our experience, gas in the wall of the intestine, mesentery and retroperitoneum, and portal vein gas, are the most important and useful radiographic features. Neither is pathognomonic; both features have been observed in patients afflicted with such entities as Hirshsprung's disease, imperforate anus, meconium ileus, small bowel atresia and following surgical repair of coarctation of the aorta. Portal vein gas can be introduced inadvertently through umbilical vein catheters.[1] Pneumoperitoneum (Figure 5) and gas in the portal venous system (Figure 4)—both generally late findings—denote a poor prognosis. When originally described, portal vein gas was felt to be universally fatal[2] but subsequently survivors have been reported in whom portal vein gas was present. Two patients with this phenomenon in the present study survived.

The disease incidence at Stanford Medical Center during 1967-1970 was 0.4 percent. This is much lower than the incidence of *unequivocal* necrotizing enterocolitis reported from the two largest series, which ranged from 0.9 percent to 3.7 percent of all admissions to Premature and Sick Infant nurseries.[3-6] The wide variation in incidence figures probably reflects population selection more than any other single factor. In the two largest series reported, the patients were admitted to special units, whereas the patients described in this paper were part of the general premature infant population.

The cause of the disease remains unknown, but several theories have been proposed: (1) Traumatic rupture of the bowel during delivery; (2) congenital defects of the bowel wall;[7] (3) infection;[8-10] (4) a localized Schwartzman reaction;[11] (5) vasoconstriction of the terminal mesenteric arterioles due to the combined action of bacterial endotoxins and elevated blood levels of catecholamines secondary to stress; (6) perinatal anoxia or hypoxia.[12-15]

There is probably no one cause. Despite the multiple etiologic factors, the pathogenesis may be similar in all cases. Mesenteric vasoconstriction is important because the necrotic areas are clearly demarcated and the tissue changes progress in a fashion similar to that of other ischemic diseases.[3-5] The surgical and autopsy findings in our series support the contention that spasm of the mesenteric vessels leads to necrosis of the bowel.

Conclusion

Early diagnosis is critical to the institution of proper therapy in premature infants with necrotizing enterocolitis. In order to make the early diagnosis of necrotizing enterocolitis, plain abdominal radiographs must be taken of all premature infants with abdominal distension, vomiting, apneic spells, jaundice, or guaic-positive stools. If the radiographs are negative, but symptoms continue, they should be repeated. Barium contrast studies of the small bowel and colon are of no value in making the diagnosis, and can be misleading.

REFERENCES

1. Miskin M, Reilly BJ: Gas in the intestinal wall and portal venous system in infants. J Canad Med Assoc 101:129-134, 1969

2. Wolf JN, Evans WA: Gas in portal veins of the liver in infants—A roentgenograph demonstration with postmortem anatomical correlation. Am J Roentgenol 74:486-489, 1955

3. Bell RS, Graham CB, Stevenson JK: Roentgenologic and clinical manifestations of neonatal necrotizing enterocolitis—Experience with 43 cases. Am J Roentgenol 112:123-134, 1971

4. Stevenson JK, Graham CB, Oliver TK, et al: Neonatal necrotizing enterocolitis. Am J Surg 118:260-272, 1969

5. Stevenson JK, Oliver TK, Graham CB, et al: Aggressive treatment of neonatal necrotizing enterocolitis: 38 patients with 25 survivors. J Pediatr Surg 6:28-35, 1971

6. Mizrahi A, Barlow O, Berdon W, et al: Necrotizing enterocolitis in premature infants. J Pediat 66:697-706, 1965

7. Boikan WS: Meconium peritonitis from spontaneous perforation of the ileum in utero. Arch Path 9:1164-1183, 1930

8. Abt IA: Fetal peritonitis. Med Clin No Amer 15:611-622, 1931

9. Blanc WA: Amniotic infection syndrome—Pathogenesis, morphology and significance in circumnatal mortality. Clin Obstet Gynec 2:705-734, 1959

10. Walhausen JA, Herendeen T, King HA: Necrotizing colitis of newborn: Common cause of perforation of the colon. Surgery 54:369-372, 1963

11. Herman RE: Perforation of the colon from necrotizing colitis in the newborn—Report of a survival and new etiologic concept. Surgery 58:436-441, 1965

12. Downing DB, Grotzinger PJ, Weller RW: Coarctation of the aorta—Syndrome of necrotizing arteritis of the small intestine following surgical therapy. Am J Dis of Childh 96:711-719, 1958

13. Singleton EB, Rosenberg HM, Samper L: Radiologic considerations of perinatal distress syndrome. Radiology 76:200-212, 1961

14. Touloukian RJ, Berdon WE, Amoury RA, et al: Surgical experience with necrotizing enterocolitis in the infant. Pediat Surg 2:389-401, 1967

15. Lloyd JR: The etiology of gastrointestinal perforations of newborn. Pediat Surg 4:77-84, 1969

Refer to: Minkowski WL, Weiss RC, Lowther L, et al: Family planning services for adolescents and young adults. West J Med 120:116-123, Feb 1974

Family Planning Services for Adolescents and Young Adults

WILLIAM L. MINKOWSKI, MD, MPH, ROBERT C. WEISS, MD, MPH, LAURA LOWTHER, RN, MPH, HELEN SHONICK, PHSWC, *and* G. A. HEIDBREDER, MD, MPH
Los Angeles

If we are to influence the numerical trends of venereal disease and of unwanted pregnancies in the young, family planning services should be made easily available to them. To encourage the widest possible and most effective use of such services requires that health professionals openly endorse their ready availability. They must foster non-judgmental attitudes, however unorthodox patient life styles may be, and provide the young with opportunities to explore their own sexual behavior.

The Youth Clinics of the Department of Community Health Services in Los Angeles are designed to meet both the immediate therapeutic and preventive health needs of our patients. Contraceptive services, abortion counseling and referrals as well as individual, group and community education are the primary pillars of our program.

There is an enormous task for all of us who are concerned with adolescents to press for sex education programs, in or out of the school system, that will include adults as well as our children.

ADOLESCENT SEXUALITY has troubled older generations for millenia: What constraints upon overt sexual behavior can fairly be imposed when pressures of youthful genital physiology and curiosity are at flood tide? Perhaps at no other time in human history has a young generation been so brazenly titillated by erotic stimuli while admonished to exercise heroic restraints upon its sexual urges. The simple fact, admittedly, is that adolescents in every generation have violated those strictures on sexual conduct established by their seniors.

While the great sexual leap forward (or backward, if you will) probably occurred after World War I,[1] the current rate of change may exceed any that went before. It is clear at least that vast numbers of young persons are now having sexual in-

From the County of Los Angeles Department of Health Services, Community Health Services, Los Angeles.

Submitted February 26, 1973.

Reprint requests to: W. L. Minkowski, MD, County of Los Angeles Department of Health Services, Community Health Services, Bureau of Maternal and Child Health, 1100 Mission Road, Los Angeles, CA 90033.

tercourse. One measure of the need for family planning services for this age group emerges from selected data on their requests for health services in California.[2] In 1971, 29,636 unmarried, teenage girls in California had therapeutic abortions —about one-fourth of the total of 116,749. In the same year in California 101,657 cases of gonorrhea were reported. Of these more than 25 percent occurred in persons 10 to 19 years old. Only one in four girls treated for venereal disease admitted to the use of any contraceptive.

In the Youth Clinic Program of the County of Los Angeles Health Department,[3] we have had a unique opportunity to observe the sexual behavior of adolescents and young adults. This program offers free general medical care and psycho-social counseling in a setting of comfortable informality and absolute confidentiality, without moral preachment. It began in January 1969 with a single clinic; now eight clinics support an annual patient caseload of 150,000. Additional thousands are turned away for lack of space and personnel.

This report is based on our experiences with the total Youth Clinic population. We do not assume that our patients are representative of all young people, though the range of racial, ethnic and socio-economic backgrounds is wide. Our family planning program, still evolving, has been responsive to patient needs. These are determined by their presenting requests for help, by solicited suggestions and by the perceptions of our staff. About 70 percent of all medical and 50 percent of all counseling problems are related to sexual behavior. These encompass the genito-infectious diseases, diagnosis of pregnancy, discussions of alternative methods of dealing with unwanted pregnancies, abortion referrals, contraceptive information and service and, in varying depth, exploration of individual sexuality. Surveys of Youth Clinic populations of divergent socio-cultural backgrounds (to be published) reveal some differences in specific sexual practices. Among all of them, however, sexual intercourse is virtually universal.

Multidisciplinary contributions to family planning services for adolescents and young adults are essential for a program whose objectives are not circumscribed by a literal definition of the term *family planning*. If we seek to help this age group avoid the unwanted consequences of uninformed or undisciplined sexual behavior, simple protection against pregnancy will not suffice. Beyond this necessary but insufficient goal we feel an obligation to offer to help young persons achieve some understanding of their own sexuality, of maleness and of femaleness. Moreover, the meaning of their interpersonal relationships, including sexual intercourse, and of both the emotional and physical consequences of their sexual behavior requires clarification for the young.

Our concept of a family planning program does not include the traditional parental function of proscribing coitus until marriage. The marital state, at whatever age, offers no guarantee of satisfying sexual experiences. Conversely, although the sexual urge may be irresistibly demanding in the adolescent, we feel no compulsion to encourage its unfettered expression for that reason alone. Our roles are complex, never purely professional, assuming the characteristics of healers, counselors, educators and, because we genuinely care about our patients, of surrogate parents, too. To achieve these objectives the special skills of nurses, social workers, health educators, community workers and physicians are required.

The concept that family planning health services for sexually active adolescents are desirable and necessary evokes both enthusiastic support and immobilizing anxiety among adults. There is little quarrel with the data documenting an epidemic of venereal disease and unwanted pregnancies. Parents are appalled by the evidence of youthful sexuality, yet secure in the knowledge of their own adolescent's innocence of this behavior. Physicians in private practice have varying exposures to the consequences of uninformed sexual activity. Out of earshot they are likely to admit the need for programs of preventive sex education and family planning services. In public, their pronouncements are often timid, cautiously testing community response. School authorities, too, fear angry parental response to suggestions that "children" should be made aware of their sexuality and that they be told of the availability of specific services in specific places. Speculation about underlying motives for these public postures may run the gamut from genuine concern for premature sexual involvements and their potential impact upon physical and emotional health to fear of real or imagined social or occupational consequences. Angry envy of the apparently greater sexual license of this generation and uneasiness about their own sexuality may also underlie adult attitudes.

We are not now concerned with an analysis of this aspect of adult behavior. Rather, we should like to share our experiences, as representatives of a conservative establishment, in developing and implementing a broad program of family planning services for adolescents and young adults.

Perhaps of paramount importance to those willing to accept the pressing need for such services for this age group is our impression that fears of community reprisal for public espousal of this kind of program may be largely groundless. The Youth Clinic Program of the County of Los Angeles Health Department has had generous support from the news media. Its staff members spread the word of its special services to some schools and private and public service organizations. Too, the publicized proliferation of free (voluntary) adolescent clinics in this and adjacent counties contributes to community awareness of a network of facilities providing health care for young persons in circumstances that do not obtain in private practice. None of these clinics, however funded, conceals its fundamental purpose—that of offering care for those health problems which the adolescent is unwilling or unable to share with parents, family physician, teachers or public health professionals.

In spite of a high degree of public visibility these clinics continue to function without generating much public protest. Rare individual parents have expressed varying anger at our policy of providing contraceptives to an "innocent" minor daughter. An invitation to visit the clinic for discussion of the complaint has always resolved the problem.

What are the attractions of these free medical clinics, privately or publicly supported, that invite the legions of young to their doors? Of least importance are the physical trappings of clinic offices. Rock music, psychedelic posters and informal staff dress may be comforting but they are dispensable. Geographic location may serve patient convenience, but seeking care when it is needed is deterred neither by distance nor by inaccessibility by public conveyance. The proximity of clinic facilities to law enforcement agencies has not discouraged visits by young patients, even by those whose overt behavior clearly suggests the influence of one or more illicit drugs. We offer no advantage in matters of waiting time, medical expertise or hospital support for those seriously ill. What does set these clinics apart from traditional providers of medical care is an attitudinal climate that convinces adolescents that we care about them as people, that we do treat them with respect and dignity, whatever their choice of life style, and that inviolable confidentiality marks the relationship between them as patients and the clinic staff.

What advice can we offer those who recognize their own community's need for adolescent family planning programs, who seek involvement in the provision of services appropriate to these needs but who recoil from the specter of public disapproval? Whether publicly or privately subsidized and whatever the scope of a projected program (medical care or counseling or both), the primary determinant is the need for health services not otherwise acceptably available. If legitimate need exists, there is every reason to try aggressively to fill it. Every effort should be made to enlist the support of health professionals, teachers, business interests, the police, parents and adolescents. National or regional data on the incidence of disease may state the problem impressively, but local statistics gathered from health departments, private practitioners of medicine, psychology and social work and from hospitals are more persuasive. When venereal infections, abortions, requests for contraceptives and youthful anxieties about sexuality can no longer be denied in one's own community, there exists the possibility for positive action. An older generation has to understand that its children are not the pristine innocents it might prefer them to be. They neck, pet and copulate with no less wonder, excitement, frustration, misinformation and fear than has every preceding generation. Some response should be made to these health needs of adolescents. Whatever the physical setting, the size and training of staff and the equipment, the young will be grateful. They can and will abide the crudest of facilities, for even these signal a genuine wish to help.

Whether medical or counseling help is offered to the young, clinic staff will be concerned about the question of eligibility for services. This is the impediment, largely artificial, at which many well-intentioned programs stumble. Local or state statute may define guidelines. Custom widely, if arbitrarily, accepts the age of 18 years as separating the mature from the immature. The law is now rapidly adapting to the press of social forces. Since artificial age barriers are easily ignored by the young, many adolescents under age 18 share health service needs with those over 18. And there

is the rub. How shall legal or social minors be dealt with? The alternatives are few. Rejection may be designed to meet local law or custom but is calculated to encourage deception about age or residence or, worse, to deny appropriate treatment to young patients.

Acceptance of virtually all patients without age requirement implies fulfillment of our roles as health healers. A policy permitting treatment of those over 12 years may afford the only opportunity to try to modify behaviors that are hazardous to teenage health. What social or legal consequences may predictably follow such a course? Our experience in the past four years should assuage anxieties about community reprisals for such an open program.

In the State of California the Emancipated Minor Act provides for treatment of minors 15 years of age or older who are living away from home with or without parental support. This law is spelled out to our patients by clearly displayed poster and by word of mouth. The intended result of these approaches is both to insure that those who qualify will receive care and, indirectly, to suggest to those who do not satisfy these preconditions how they, too, may be eligible for our services. Since our program is designed to meet health needs that the young perceive as inadequately met elsewhere, we do not ask for proof of age or of residence. It is possible that we do accept as patients some who are, indeed, unemancipated minors. While we have no wish to violate the law, however arbitrary its provisions may seem, our first concern is for the adolescent in need of help.

Our program continues to serve youthful demands for health services that regularly exceed our capacity to respond. What initial fears we had that angry, vindictive parents would protest our presumptuous decision to care for their sons and daughters without their consent have vanished. The sum of complaints from parents or other citizens who (1) resent our intrusion into an area of health care traditionally assigned to the family or (2) are offended by our acknowledged intent to provide specific services in the field of sex behavior, has come to only half a dozen telephone calls. Those who called were distressed at their child's sexual behavior and at our unshakable resistance to divulging the confidences of minors. Yet there have been no threats of litigation or even of mounting a campaign to close our doors. It is possible that inertia may explain this apparent reluctance to verbalize dissent with our program. From some parents we have received private confessions of relief that someone else is prepared to assume responsibility for their children's education in human sexuality as well as for protection against the unwanted consequences of their explicit sexual behavior.

Youth Clinic Family Planning Program

All of our clinics share the same basic family planning philosophy and each has freedom to develop its own operating methods. Every sexually active patient is questioned about her (less often, his) use of contraception. One primary focus is on the patient who comes in to ask for a pregnancy test. She is likely to be under 20 years old, single, pregnant for the first time, alone and admittedly desperate for assistance. The circumstances are ripe for counseling intervention. At no other time is she so receptive to the suggestion that her life style merits critical review. If for no other reason, it is important to equip her to avoid repetition of her current concern for pregnancy. Before the pregnancy test result is available, she is invited individually or with a variable number of her peers to express her feelings freely about pregnancy. Her presence at the clinic provides an easy entry into a discussion of her sexuality.

For most of our young patients numbers are comforting when similar anxieties are shared. Moreover, the group experience facilitates her groping search for the meaning of her own sexual behavior. She discovers, for example, the multiplicity of coital motives that have little or nothing to do with sharing a warm, loving, human relationship. The ploy of testing her personal explanations for an unplanned pregnancy against the sympathies of others in a similar situation rarely achieves its intended result. Confrontations with the unyielding realities of the observations of others is at once bruising and reassuring. Whatever the motives for having unprotected coitus or for a specific disposition of an established pregnancy, they prove not to be unique. This revelation, too, can be reassuring to anxious and guilty patients. Moreover, the empathic but firm hands of the group leaders are always at the reins. They listen, elicit beliefs and attitudes, encourage participants to talk freely and to respond to each other. At the same time, they provide answers as well as reassurance.

The alternatives available in dealing with each

patient's problem are presented without bias. Misconceptions are corrected, anxieties are allayed and reasons for individual choices are examined. The objective is to encourage each patient to make her own decision. Most girls are already committed to therapeutic abortion. If preferences remain unshaken, patients are referred to an institution or a private physician for appropriate surgical intervention. (This referral process will be discussed later.)

These group and individual sessions elicit observations that merit discussion. Ignorance of basic anatomy and reproductive physiology is striking. Neither frequency nor duration of sexual activity nor educational level necessarily bears any direct relationship with accurate knowledge or understanding of human sexuality, including one's own. The legacy of our failure to educate before physiologic maturity can be illustrated with innumerable anecdotes. A few will suffice to highlight the tragedy of the uninformed. "But I always insist that he (one or more partners) pull out before he comes." "We were careful about the time of our sex. It was always during my safe period, you know, around the middle of my month." "Everytime I had sex, I would douche right after." "But I didn't think a girl could get pregnant unless she had an orgasm." Perhaps the most common response to the question of failure to use a contraceptive was, and continues to be, "I just didn't think it would happen to me."

Many of our female patients deny any orgastic experience. A lesser number of males, while confessing orgasms, express pallid enthusiasm for these experiences. Such admissions are not difficult to elicit. On the contrary, they are freely offered in as little time as is required to convey sincere concern for the quality of their sexual behavior. When the sexual attitudes of these unsatisfied males and females are pursued, what becomes clear is that they are often reluctant sex partners, compelled to participate by pressures they feel powerless to control. Their sexual acting out appears to reflect psycho-socio-cultural forces that have interfered with or distorted the development of confident gender identity. Their responses to the simple question, "Why do you have sexual intercourse?" are commonly concerned with warm, loving human contacts, peer approval, and identity as women and men. A few of their statements will serve to illustrate this point. "If I say no to my boy friend (old man, cat, dude), he'll find himself another girl (woman, chick)." "How can I say no to him?" "He says if I really love him I'll go to bed with him." "It makes me feel like a woman to make love." "But all my friends are doing it." "I feel sorry for him." From the males we hear these comments. "I'd be ashamed to tell my friends I don't really like balling a chick I don't dig." "It's like smoking grass; everybody's doing it, so why not me?" "I dig sex."

The simple suggestion that one can say no to an offer to go to bed is startling to some of our patients. That rejection of such an invitation may be the antithesis of their notions about womanhood and manhood, that it may indeed represent the beginning of mature, responsible, independent behavior, is not difficult for them to accept intellectually. We do not yet know how many will be able to translate this understanding into everyday behavior. Discussion in groups, with or without males, has the dual advantages of economy of time and of personnel and of peer support as well as merciless confrontation with reality.

For those who are made uncomfortable by group scrutiny or who require more time for decision, individual sessions are scheduled. A few males attend with their partners. They participate willingly, if worriedly, usually admitting failure to discuss contraception with their women, much less urge it upon them. "I figured all girls take the Pill" expresses both a common myth and an unquestioning readiness to renounce personal responsibility for protection against pregnancy.

Although a girl usually is able to talk comfortably about pregnancy in others (or even in herself in the abstract) knowing of her own pregnancy forecloses retreat into fantasy. For this reason the pregnancy test results are given each girl individually. For some patients there is no hesitation in declaring for a therapeutic abortion. For them, discussion of alternatives and feelings is brief, swiftly moving to specific arrangements for operation. For others, however, even though they may express a wish to have abortion, there is sufficient uncertainty, anxiety and guilt to make them welcome an exchange with a counselor. In such cases we almost invariably find ourselves in accord with the patient's evaluation that the time is not appropriate to bear a child. There are a few who have a stable, unwed relationship with a loving partner. For them the impediment is often rooted in the conflict of generations. Social (parental) pressure against rearing a child outside of mar-

riage put them under stress. Their intellectual justifications are opposed by cultural abjurations. Our tack is to help them reach the least compromising decision.

Often the purpose of the patient's first visit to the clinic is to get help in preventing pregnancy. With few exceptions it is the Pill she seeks. Only rarely does a patient simultaneously say that she is a virgin and ask for a way to avoid pregnancy. The others, with widely ranging coital histories, admit to using a variety of contraceptive measures with inconstant regularity. As often as not, faith in fate to intervene in the union of sperm and ovum has been the method of choice for months. In view of the frequency with which unscheduled, unimpeded release of male gametes occurs in our patient population, the wonder is that more pregnancies do not result.

Whatever the reason for visiting the clinic, we use every opportunity to inform our patients about contraception. The two most reliable birth control methods, the Pill and the intrauterine device, are most commonly requested and most frequently generate questions about safety and comfort. Alternative measures are reviewed for the patient when individual coital practices suggest that constant protection is not necessary. The diaphragm is rarely asked for, and because our early efforts to encourage its use were unfruitful, our current mentions of it are not very persuasive. We have found widely shared objections to vaginal foam or condoms on the grounds of (1) interference with both spontaneity and naturalness of coitus, (2) diminished tactile pleasure for both partners and (3) for some males, an unpleasant gustatory experience. That it protects against genitourinary infections fails to attract many males to the rubber sheath. The apparent indifference of males—and some females—to these communicable diseases may have various psychological roots, but the concept of antibiotic infallibility is probably the main factor. For the male especially, the sequence of symptoms, diagnosis, treatment and, with little delay, no symptoms, is cogent evidence that his infection has not been a hazardous experience. In recent months we have shifted the focus of our condom campaign to the female, attempting to convince her that 0.003 inch of latex or lambskin or gut may determine her future ability to bear children. We cannot yet assess the results of this effort.

Abortion Referrals

Our abortion referral services have evolved slowly since the days when the first of our patients were sent to Mexico. We are ever grateful to the Clergy Counseling Service for Problem Pregnancies for its courage in defending abortion rights for women. Beyond that contribution, it pioneered in helping women to resolve problem pregnancies and intervened in establishing cost and quality controls for abortion in a foreign country. Although we had misgivings about urging patients to accept abortion help at distances so remote from us, our initial experiences, born of sheer necessity, were satisfactory.

The availability of abortion has changed dramatically since that time. Reticence to perform this has yielded to what appear to be changes in public attitude. Now, few hospitals refuse to permit abortions except for reasons of religion or conscience. Although concern for detection remains an important issue, especially for many adolescents, most patients prefer a hospital close to friends and family. By California law the pregnant minor is considered an adult. Hence she is not required to have parental consent for abortion. In recognition of the high cost of a therapeutic abortion, the California Department of Public Social Services has opted to certify patients for temporary coverage under Medi-Cal. Once the operation has been completed, eligibility for this service ends.

As we became more comfortable in the abortion setting, we began to assume increasing responsibility for managing our patients from the initial request for a pregnancy test through counseling to the post-abortion review. Questions of the intensity and duration of the emotional impact of an abortion remain to be answered more fully. No less important than physical and emotional evaluation after abortion is the urgency of emphasizing contraception before resumption of coitus. Even with a high rate of post-abortion return visits, we are not likely to persuade every female to accept reliable protection against another pregnancy immediately following an abortion. The patient's commitment to post-abortion celibacy may be so resolute at that time that she may believe she will not need contraceptive help. Moreover, without special efforts designed to expose motives for pregnancy—wanted and unwanted—in young patients, the most intensive informational programs will fail. In reality, the

rate of return to our clinics following abortion has been discouraging. For this reason we are now exploring new, if obvious, methods of inviting continuity of care. However skillful we may become in luring patients back after an abortion, we shall not succeed in insuring pregnancy protection until they understand "where their heads are at"—that is, what their sexual behavior means to them.

Some idea of the roots of their risk-taking has emerged from discussions with our pregnant patients and with those who simply by chance have not become pregnant. In general what we have learned is in basic agreement with the observations of other investigators.[4] Although subconscious and unconscious determinants play a role, these are not easily measured. Lack of accurate information and more importantly, mythology, are common factors in unprotected sexual exposures.

Contraception

Family planning services for the non-pregnant make the heaviest demands upon our program. Although we encourage males to participate with their partners in decisions about contraception, multiple partner relationships, usually casual, and the absence of reliable and acceptable birth control measures for males place the burden of pregnancy prevention on the female. With few exceptions males and females alike assign this responsibility to the woman. When coitus is infrequent—that is, once a week or less—we urge the use of vaginal foam with a condom, or of the diaphragm. About 90 percent of our patients request the Pill. Whether or not there has been a previous pregnancy we are now more frequently recommending use of the intrauterine device. The smaller devices are more comfortably introduced. For the first two or three months following insertion of an IUD, vaginal foams or birth control pills may be provided to protect against early failure of the coil. Patients requesting contraception are screened by a member of the clinic staff in the routine way: name, address, telephone number, age and a brief review of the reason for seeking help. A nurse or health educator discusses the available birth control measures with patients, either individually or in groups. The focus is on elementary reproductive physiology, methods of action, and of use, safety, convenience and reliability. Since medications are offered without charge, cost is not a factor in the patient's choice of method. While waiting to be examined by a physician, each girl completes a one-page questionnaire related to menstruation and pregnancy, previous contraceptive experience and past health. The physician evaluates this information, examines the patient and prescribes the appropriate method of birth control. The examination is not complete but does include the breasts, blood pressure, superficial blood vessels and the pelvis, and a search for gross endocrinopathy. A Pap smear repeated at yearly intervals and, except for the rare virginal patient, endocervical and vaginal swab specimens for gonorrhea plated directly on Thayer-Martin medium, are routinely done.

For those who are taking the Pill, not more than two packets are given at the first visit. We insist on starting the Pill on the fifth day of menses unless convinced that the patient cannot be trusted to protect herself until her next period. In such cases we may extend the first day of Pill use to the tenth day. For those who begin use of oral contraceptives on the fifth day of menses, we assume that reliable protection against pregnancy exists immediately. With a late start, however, from the sixth to the tenth day of a menstrual cycle, we urge the use of vaginal foam for one week. Side effects from the Pill are described in detail and patients are encouraged to return at any time if questions about symptoms arise. Since side effects are usually mild, we see most of our patients in one or two months when they ask for additional supplies. At that time, and with subsequent return visits every three or four months for renewal of medication, we check weight and blood pressure and inquire about complications of Pill use. Rarely have we had to suggest a change in contraceptive. Our standard preparation is Norinyl® 1 + 50 28 Day. For recurrent breakthrough bleeding we have found Ovral® a satisfactory substitute.

Our experience with the IUD, principally the Dalkon shield, has demonstrated its utility in young, often nulliparous patients. No local anesthesia is used. Sometimes, though not often, an urgent request for removal is made because of cramps or heavy bleeding or the contusion of the partner's penis by a string. Delayed complications, including failures, infections, escape and perforations have been notably few. Since few of our Youth Clinic physicians have had gynecologic training, not many are experienced in insertion of the IUD. Brief training under expert supervision provides the necessary skill and confidence to perform this procedure.

Evaluation

The family planning component of our Youth Clinic program continues to evolve. Its successes can be measured in humanist terms. Of the first order are the counseling and services we offer those who are pregnant and eager for help in resolving a major crisis. We do not presume to know the wisest choice for any patient. If group interaction fails to generate a decision, time for individual discussion is always available. Although we regard the unwanted pregnancy as a significant life crisis, we do not feel that an abortion necessarily leaves an indelibly destructive imprint on body or mind. An important, though less urgent, function is the advice to the large numbers of sexually active women unprotected against an unwanted pregnancy until we provided contraception. We are reassured by the consistent return of most of our patients for refills of oral contraceptives. It is those we do not see again who are cause for concern. Thus, abortion counseling and contraceptive services are the two main pillars of our program. Although we support the ready availability of abortion, each one performed is a reminder of a failure to provide reliable contraception. Both within the clinic and in the community our efforts are directed toward the sexually active woman in risk of pregnancy. Almost every female, whatever the reason for her clinic visit, is questioned about her sexual activity and use of birth control methods. A reliable contraceptive is urged upon all those in need. Acceptance usually follows adequate explanation of the benefits and the risks. There are some, however, who remain committed to their sexual experience without artificial impediment. Concerns for health, whether well based or not, and for sexual naturalness are the bases for rejection of conception controls.

In meetings of community groups of all kinds we define the problem of unwanted pregnancies in public health terms and affirm the urgency of support for free adolescent clinics and for the widest dissemination of birth control information. We eagerly accept invitations to give advice to senior and junior high school and college audiences. In spite of occasional protests that we encourage promiscuity among students, we pursue our goal to inform those who are currently, or are soon to become, sexually active that protection against pregnancy and venereal infections does exist and that treatment for either or both conditions is available to them confidentially and without cost. Further, student questions invariably involve us in discussions of appropriate sexual behavior for adolescents. We avoid lofty talk of morality, suggesting only that our basic concept of immorality encompasses any exploitative behavior in interpersonal relationships. Among other points we press home it that neither femininity nor masculinity can be called into question if one rejects the opportunity to have sexual intercourse; that coitus is far more enjoyable when genuine affection and a sense of responsibility for self and for others are part of a relationship. In every segment of the community we push the issue of full sex education in the schools, for students, parents and teachers.

Our gravest concerns are for the patients referred for abortion. Since few of them return for follow-up, we have little appreciation of their response to the experience. Are they treated with understanding of their needs for compassion and respect as well as for good surgical skills? Will they be seen again after abortion, for necessary physical or emotional intercession? Has our pre-abortion emphasis on future contraception been reaffirmed? From those we do see after abortion, we have the impression that the abortion experience, if often impersonal, is not seriously traumatic. Fears and anxieties that surfaced initially appear to evaporate quickly once the event is over. This may reflect skilled pre-abortion counseling or a high degree of adolescent resiliency or a combination of these factors. Are those who do not return to us coping well or poorly? That question plagues us and underlies our eagerness to develop more effective techniques for persuading our patients to visit us after abortion.

Our wish to exercise a measure of control over the quality of operating conditions led us to form an abortion committee. Its function is to identify, by on-site visits, those hospitals with acceptable abortion procedure standards. This provides health department and other agencies or individuals referring patients for abortions some basis for selection of a hospital. Physicians who do not use an approved hospital are not included in our referral lists. While this policy offers us a degree of comfort, we have no continuous monitoring of these hospitals.

REFERENCES

1. Rubin I: Is there a sex revolution? Sexology 32:220-222, 1965
2. Fact Sheet, Facts of Life in California—1972, Berkeley, Calif. Public Education and Research Committee of California, 1972
3. Minkowski Wm L: The County of Los Angeles Health Dept. Youth Clinic. Am J Public Health 61:757-762, Apr 1971
4. Sandberg EC, Jacobs RI: Psychology of the misuse and rejection of contraception. Am J Obstet Gynec 110:227-242, 1971

Refer to: Rosenberg RN, Mendoza G: Idiopathic acute symmetrical polyradiculoneuritis—The Landry-Guillain-Barré-Strohl syndrome—Pediatric Grand Rounds, University of California, San Diego, and University Hospital of San Diego County (Specialty Conferences). West J Med 120: 124-130, Feb 1974

Specialty Conference

Participants

ROGER N. ROSENBERG, MD
GUILLERMO MENDOZA, MD

Taken from the weekly Pediatric Grand Rounds held at the University Hospital of San Diego County, University of California, San Diego, School of Medicine

Idiopathic Acute Symmetrical Polyradiculoneuritis

The Landry-Guillain-Barré-Strohl Syndrome

DR. MENDOZA:* This was the first University Hospital admission for a 13-year-old Mexican boy who was in excellent health until, 11 days before admission, he became febrile and complained of myalgias and headache. The illness was brief and the patient was entirely well within a few days. Four days before admission, however, the patient had sudden weakness of his arms and legs symmetrically without fever. Only 24 hours elapsed between the onset of weakness and quadriparesis which confined him to bed. At first his oral intake remained normal but gradually he had increasing difficulty swallowing whole food, and his intake became limited to fluids. He was first admitted to hospital in Tijuana for three days but was subsequently discharged and because of progressive respiratory failure was advised to come to the emergency room of University Hospital, San Diego.

The youngster had never been immunized, had no history of ingestion of canned foods, wild berries or shellfish and had had no tick, spider or snake bites. The remainder of the history was non-contributory.

*Guillermo Mendoza, MD, Intern in Pediatrics.

Reprint requests to: R. N. Rosenberg, MD, Professor and Chairman, Dept. of Neurology, The University of Texas Southwestern Medical School, Dallas, Texas 75235.

The patient was evaluated in the emergency room, found to be paralyzed symmetrically below the shoulders and to have very shallow respirations. At rest, he could barely count to 3 before taking a breath. His chest was hyperresonant and had diminished respiratory sounds. The use of accessory muscles of respirations was evident. The abdomen was soft and not tender, and the bladder could be palpated at the level of the umbilicus. The patient then spontaneously voided 750 ml of urine. Rectal tone appeared diminished. The patient remained alert and apprehensive. The cranial nerves appeared to be intact. He was completely areflexic. No muscle atrophy could be discerned. Sweating was noted over the entire body. Pain, temperature and vibratory sensory responses were intact. The patient complained of minimal calf tenderness which was relieved by positional change.

An arterial blood gas determination in the emergency room with the patient breathing 40 percent oxygen showed pH of 7.45 and pO_2 of 145 and pCO_2 35 mm of mercury. Vital capacity at this time showed a value of 250 ml.

Tracheostomy was performed without complication. At first a Bird ventilator was used, but soon a change was made to an Emerson volume

TABLE 1.—*Laboratory Data on the Cerebrospinal Fluid and Vital Capacity*

	Cerebrospinal Fluid				
			Leukocytes		
Date	Glucose mg/100 ml	Protein mg/100 ml	No.	PMN/mono Percent	Vital Capacity, ml
12-11-72	 93	60	18	40/ 60	....
12-14-72	 76	51	2	50/ 50	250
1- 4-73	 70	258	1	0/100	400
1-19-73	.... ..	...	..	.....	750
2- 7-73	.... ..	...	..	.....	1100
2-13-73	.... ..	...	..	.....	1550
2-21-73	.... ..	...	..	.....	1700
4-21-73	 60	53	2	50/ 50	....

respirator. Virtually no supplementary oxygen was required. Clean techniques were emphasized to prevent pulmonary infection. No antibiotics or steroids were given. General physical therapy including chest physiotherapy was initiated at once. Periodically, cultures were made of tracheal aspirates, and x-ray films of the chest were taken. The patient was able to take a liquid diet after a short time. Despite maximal fluid nutrition the patient's body weight decreased about 300 to 500 grams a day. Emotional support was emphasized and the patient bore the ordeal commendably.

Neurological recovery is partially summarized by the measurement of vital capacities (Table 1).

Over the three months he was in the hospital, gradual increase in muscular ability to flex his fingers, internally rotate his arms and eventually to abduct his arms was observed, as well as increasing return of diaphragmatic movements. Data on sequential spinal taps are summarized in Table 1. Nerve condition studies, done one month after admission to hospital, showed no conduction across the left medial and peroneal nerves. Serum complement fixing and hemagglutination inhibiting titers for poliomyelitis virus types 1, 2 and 3 were negative. Fluorescent antibody titer to the Epstein-Barr virus was 1:50 and the ox hemolysin value was 1:320, both diagnostic of recent infection with the Epstein-Barr virus.

Following the return of the vital capacity to normal limits about two months after admittance, cannulae were removed without complications. The patient was discharged after more than three months in hospital. Flexor, extensor and abductive-adductive movements of both hands had returned and he had some proximal arm movements. There was some restoration of proximal and distal leg movements but the patient was not able to overcome gravity. Results of sensory examination were normal, as were bladder and bowel functions.

Differential Diagnosis

DR. ROSENBERG:* The patient presented by Dr. Mendoza represents the syndrome of acute paralytic lower motor neuron disease. The considerations in differential diagnosis that we faced in the evaluation of this patient were poliomyelitis, diphtheritic polyneuropathy, botulism, acute myasthenia gravis, acute transverse myelitis, and acute idiopathic polyneuritis. I think poliomyelitis is a reasonable possibility in this patent as the patient was from Mexico and was not immunized, but there are arguments which can be raised against poliomyelitis. We think of the onset of paralysis with poliomyelitis as a type of paralysis occurring with fever, but our patient, as best we can document it, had an afebrile type of paralysis. The paralysis was a symmetrical and an ascending one. With poliomyelitis I think more of an asymmetric, random paralysis. Also, the patient had an albuminocytologic dissociation (as is shown in Table 1) and I would have expected with this degree of widespread paralysis due to poliomyelitis, more of a pleocytosis in the cerebrospinal fluid. For all of these reasons and the low serum titers, I think that poliomyelitis is not likely. Acute myasthenia gravis is unlikely in the absence of significant cranial nerve paralysis, especially of musculature innervated by cranial nerves 3, 4 and 6. The patient was also totally areflexic—again unusual for myasthenia. Botulism, I think, has to be considered, but again it has to be just considered. There was an absence of significant cranial nerve impairment. The patient had neither pupillary abnormality nor visual acuity impairment, which are hallmarks of botulism. In diphtheritic polyneuropathy, cranial nerve disease would be prominent and would appear early in the patient's course relative to an ascending symmetrical polyneuritis. Our patient did not conform to this pattern of paralysis.

Acute transverse myelitis can be very difficult to distinguish from acute symmetrical polyneuritis. It can present as an ascending symmetrical paralysis, but later in his course I think we would have expected some upper motor neuron signs such as hyperreflexia, Babinski's sign and

*Roger N. Rosenberg, MD, formerly Division Chief, Division of Child Neurology, Associate Professor of Neurosciences and Pediatrics, UCSD; now Professor and Chairman, Department of Neurology, The University of Texas Southwestern Medical School at Dallas.

spasticity. A sensory level might also be present. For all these reasons, the conditions noted in this patient corresponded best to those of acute symmetrical polyneuritis, and thus the case provides us an opportunity to discuss the clinical manifestations and the pathogenesis of this very interesting neurological problem.

Clinical Manifestations

The syndrome was initially described in France in 1859 by John Baptiste Octave Landry, who reported upon an ascending form of paralysis, and it is his description that seems to correspond best to what Guillain, Barre and Strohl subsequently described.[1,2] Guillain's contribution was to emphasize the albuminocytologic dissociation and the high protein content and minimal cellular response in the cerebrospinal fluid.

We are discussing a syndrome which seems to occur at any time of life. Polyneuritis is well described in the immediate neonatal period in the neurological literature, and it is seen throughout life and into the ninth decade. There seems to be a trimodal distribution. The incidence of the disease is high in the first decade of life, and it peaks again in the second and sixth decades.

About 40 percent of patients presenting with acute ascending polyneuritis have an infectious syndrome, usually viral in association, either during or before—sometimes as much as two months before—the onset of paralysis. Viruses cultured from stool have been varied in type. Adenovirus, coxsackie, parainfluenza, influenza and Epstein-Barr viruses have been associated with this syndrome. The first symptom of illness in this syndrome in about three-quarters of patients begins with lower extremity weakness, and about one-third some sensory complaint as the initial manifestation. The weakness, beginning in the lower extremities, ascends as Guillain and Landry described. The sensory involvement is much less prominent than the weakness in this form of polyneuritis. Paresthesias, numbness, pinprick loss and myalgias are seen in about 30 percent of patients on admission. Results of the sensory examination are positive, eventually, in about 70 percent of patients. The literature points out that this syndrome is mainly a motor paralysis; but if a careful sensory examination is done, it can be shown that many patients have some sensory abnormality, though usually mild and transient. Thus the syndrome consists of an ascending, symmetrical, areflexic paralysis which begins in the lower extremities and ascends subsequently to involve the arms. About 25 percent of patients have weakness only in the lower extremities. Changes referable to the cranial nerve involve mainly cranial nerves 7, 9, and 10. Facial weakness of the bulbar innervated muscles causing difficulty with swallowing and coughing are commonly encountered. It is this type of change that has to be identified early, for the patient who has difficulty with coughing is usually going to get into respiratory difficulty early, with aspiration pneumonia developing. About 20 percent of patients with this syndrome—and usually these are also the patients who have bulbar weakness—clearly have respiratory insufficiency. Early tracheostomy is necessary in such cases to assist with ventilation during the first two months of illness. The reduction in mortality from about 20 percent to about 5 percent in the past three decades is attributable to early identification and prompt tracheostomy.

The cerebrospinal fluid (CSF) is characteristic in this disorder. There is a minimal cellular response, usually a lymphocytic response, and elevation of protein content. Osler and Sidell emphasized an arbitrary upper limit of 10 cells per cu mm as still being compatible with this syndrome.[3]

The overwhelming majority of patients with this disorder do quite well. They will have a complete return of neurologic function and be able to leave the hospital under their own ambulation. About 10 percent of patients continue to have disabling deficits. Mild neurologic involvement occurs in about 20 percent of patients.[4,5] The patient presented today, I think, represented one end of the spectrum of severe paralytic illness. At the other end is the patient who has a viral-like illness and has some nonspecific weakness for a few days. Those who are admitted to hospital with this syndrome usually improve and are walking again within two or three months after the onset of illness.[3-5]

An unusual variant seen in post-infectious neuritis is a relapsing course of polyneuritis but a constantly elevated CSF protein.[6] Another variant is polyneuritis which becomes steroid-dependent.[6] In general, steroids are not helpful in acute polyneuritis of post-infectious type. An occasional patient has been described with acute polyneuritis who was given steroids and rapidly improved. Exacerabation and remission with steroid responsiveness occurs in a small percentage of patients with acute polyneuritis; the response may represent a different disease entity.

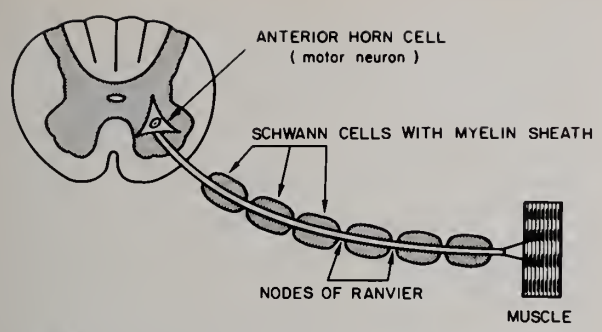


Figure 1.—The spinal cord is shown in cross-section. The motor neuron is in the ventral horn of the cord and its axon innervates a muscle fiber. The axon is normally myelinated by Schwann cells which are interspersed with gap-regions referred to as nodes of Ranvier.

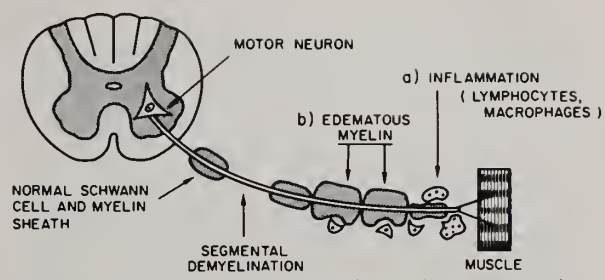


Figure 2.—The spinal cord is shown in cross-section with the motor neuron in the ventral horn. The motor nerve axon illustrates the pathologic changes in the myelin sheath seen in acute idiopathic polyneuritis: (a) the early inflammatory response; and (b) edema and phagocytosis of myelin by macrophages. Segmental demyelination is a later stage in the process showing loss of Schwann cell and its myelin leaving a widened node of Ranvier.

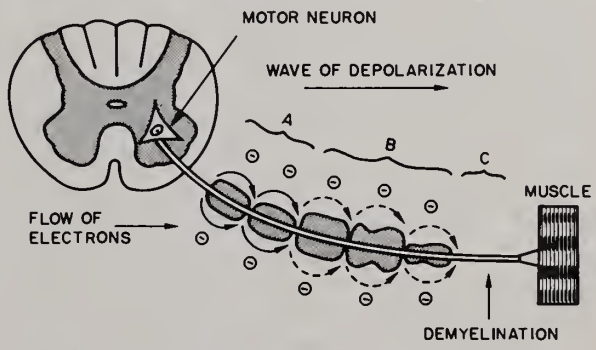


Figure 3.—Impairment in saltatory conduction down a motor nerve fiber. Region A shows a normal conduction velocity due to the normal rate of the flow of electrons in a region of the motor nerve that is myelinated and has intact nodes of Ranvier. Region B has slowed conduction velocities due to myelin edema and hypomyelination. A total blockade of electrical conduction is seen in region C where the motor nerve axon is entirely demylinated.

Pathogenesis

Acute idiopathic symmetrical polyneuritis is a disorder of unknown cause. The strong history of antecedent viral infection in 40 percent of cases and the isolation of virus or elevation of the serum viral titer in many cases suggest that it is primarily a syndrome of viral origin. Further evidence also suggests it may be a secondary immunological disorder.[7-10] Perhaps, then, after viral infection of the host, there results an immunological cross-reactivity of a virus-coat protein with a protein in peripheral myelin which results in subsequent demyelination. Anatomically, we are dealing with a disorder which mainly affects the Schwann cell which synthesizes and maintains peripheral nerve myelin (Figure 1). The ventral root axons of the anterior horn cells which innervate voluntary striated skeletal muscle and their Schwann cell which invests these motor axons with myelin are primarily involved. To a lesser degree the Schwann cell of the sensory fibers which carries afferent impulses back into the spinal cord is also affected, resulting in sensory fiber demyelination.

The initial pathologic response is a severe inflammatory reaction in which round cells accumulate around veins in the peripheral nerves. Histologic sections of peripheral nerve near the point where the motor and ventral roots fuse show a significant lymphocytic infiltration into the peripheral nerve fibers. Subsequently, there is edema of the myelin sheath and fragmentation of the myelin with demyelination (Figure 2).[7]

Normal conduction of nerve action potentials from the anterior horn cell to muscle occurs by saltatory conduction which is a wave of electrical depolarization due to a flow of electrons on the outer surface of the myelin sheath as well as in the axoplasm. The electrical depolarization depends on the maintenance of nodes of Ranvier or interspaces of a narrow and precise degree between Schwann cells. Conduction of this type requires the integrity of the myelin sheath investment and proper interspaces between these nodes. If there is deficient myelin, there can be no saltatory conduction or jumping of a wave of electrons from one node to another down the alpha motor nerve fiber. There will be a conduction block to the flow of electrons from that point on. As a result of edema, the saltatory conduction wave may be slow; and if there is a great deal of edema, there will be inability to generate a nerve action potential at all (Figure 3). This is consistent with the conditions noted in patient under discussion at the time of admission. The clinical expression of the slowing in conduction velocity or conduction blockade is weakness or paralysis.

It is also important to consider the state of the anterior horn cell, the lower motor neuron. The anterior horn cell undergoes a process known as chromatolysis as a result of disease of its peripheral axon. The cell body becomes enlarged and the nucleus becomes eccentric. There is a loss of Nissal staining, which represents depolymerization of the polyribosomes of the endoplasmic reticulum. The anterior horn cell undergoing chromatolysis is clearly impaired but is potentially retrievable if the distal disease process resolves—that is, if edema resolves, if inflammation resolves, if remyelination again ensues—with reestablishment of functional muscle innervation.

Thus, in summary, the postulate is that there is a primary viral infection, followed by immunologic cross-reactivity of a virus-coat protein with a myelin protein and that immune complexes are established in the peripehral nerve, causing tissue damage and edema. Macrophages and histiocytes are then mobilized in order to remove the edematous, damaged myelin. The process can go on to complete destruction of the axon and the Schwann-myelin investment, and at this point, recovery would depend upon the regrowth of a new growth cone of the axon to reinnervate a muscle fiber. If the disease process is arrested at this point and the muscle fiber is rennervated, the anterior horn cell will again revert from a chromatolytic to a normal morphology.

Indirect evidence which suggests that this is secondarily an immunologic disorder was presented in the paper by Rocklin et al[8] in which they looked for the presence of macrophage migration inhibitory factor in lymphocytes from patients with acute polyneuritis. They incubated peripheral nerve antigen with lymphocytes obtained from patients with a variety of peripheral nerve diseases, and then incubated the supernatant with guinea pig macrophages placed in a glass capillary tube to see if there is inhibition of macrophage migration. If there is inhibition of migration, then the sensitized lymphocyte presumably has made a soluble factor which prevents migration. They looked at patients with the Guillain-Barre syndrome, alcoholic polyneuropathy, diabetic polyneuropathy and a variety of other peripheral nerve diseases. Patients who had the Guillain-Barre-Strohl syndrome (four of the seven patients) had an inhibition of macrophage migration, whereas lymphocytes of patients with alcoholic, diabetic and other forms of neuropathy did not. Thus Guillain-Barre (acute polyneuritis) patients have lymphocytes which are sensitized to peripheral nerve antigen.

Furthermore, the neuropathologic features of this syndrome look very much like those of an experimental condition known as experimental allergic neuritis. If one injects peripheral nerve antigen with Freund's adjuvant into experimental animals, there occurs a characteristic lymphocytic infiltration and edema of myelin and demyelination which is characteristic of the human form of the disease. Further, one can take lymphocytes from experimental animals which have experimental allergic peripheral neuritis and passively transfer the syndrome into other experimental animals by injecting the sensitized lymphocytes. Lymphocytes from animals which have experimental allergic neuritis as well as lymphocytes from patients with acute polyneuritis will also demyelinate peripheral nerves placed in tissue culture.[9]

Recently a patient was described who had acute polyneuritis and acute nephritis. Immunofluoresence studies of his kidneys showed immunoglobulin IgM and IgG in a fine granular pattern. Cell mediated hypersensitivity was demonstrated both to kidney and to nerve antigens, and humoral antibody to the same antigens was also found.[11] Thus evidence is accumulating to indicate that the dymelination occurring in this syndrome may be immunologically based.[7-11]

I would like to mention another type of polyneuritis which entered into the differential diagnosis of our patient. That is buckthorn polyneuropathy.[12] The ingestion of the berry of the buckthorn plant produces a polyneuropathy and a clinical picture indistinguishable from acute post-infectious polyneuritis. Transverse sections of peripheral nerve demonstrate extensive fragmentation and edema of myelin.

In an interesting paper by Ramos-Alvarez and coworkers,[10] two unique neuropathological entities were described which clinically resemble post-infectious acute polyneuritis. These investigators described 32 patients seen in the Hospital Infantil in Mexico City between 1962 and 1968 who had poliomyelitis and 24 patients who had noninflammatory diseases involving the spinal cord. All of them had clinical manifestations just like those of post-infectious acute polyneuritis. Several of these patients were felt not to have post-infectious acute polyneuritis, but rather cytoplasmic neuronopathy

or nuclear neuronopathy. The authors contrasted the Landry-Guillain-Barré-Strohl syndrome with cytoplasmic neuronopathy and nuclear neuronopathy. The interval between onset of paralysis and death in the cytoplasmic and nuclear neuronopathies is much shorter, indicating a more fulminant type of disorder than post-infectious acute polyneuritis. This may be the only distinguishable clinical feature. The fulminant onset—usually an upper respiratory tract infection and then weakness involving the lower extremities with an ascending, afebrile paralysis—is characteristic. The CSF changes do not distinguish between these three types of neuropathologic entities. A high CSF protein and a minimal cellular response was seen in many patients with all three disorders (acute polyneuritis, cytoplasmic and nuclear neuronopathies).

Neuropathologic examination in nuclear neuronopathy demonstrates that the anterior horn cell is shunken and the nucleus is pyknotic and filled with argyrophilic inclusions. In acute polyneuritis, (Guillain-Barré) there is some tendency to chromatolysis, but by no means is it as severe as in cytoplasmic neuronopathy, where the Nissal staining is almost completely gone, the nucleus is eccentric, and the anterior horn cell is severely swollen. Thus, although the neuropathologic changes of these three disorders of the lower motor neuron, its axon and the myelin sheath appear distinct, in clinical manifestations they are almost indistinguishable from each other.

I have tried to emphasize that we are discussing a Schwann cell disease which results in segmental demyelination, slowing of motor nerve conduction velocities, and denervation. With progression of the disease process, there is later destruction of the motor axon and its cell body, the anterior horn cell.

There is another series of peripheral neuropathies which are classified as axonal dystrophies. The best example of these are acute lead polyneuropathy, and polyneuropathy induced by drugs (thalidomide, dilantin, vincristine, INH, furadantin and acrylamide). Two well-documented examples of drug neuropathy are due to vincristine and acrylamide. These types of neuropathy seem to involve the microtubular protein (tubulin) which is a 60,000 molecular weight monomeric subunit which polymerizes to form two important structures in the peripheral nerve, the microtubule or the neurotubule and neurofilament. These structures are concerned with facilitative transport of enzymes, neurosecretory vesicles and protein. Vincristine and acrylamide bind to and disrupt these structures, and thus impair axoplasmic flow.

The first demonstration of axoplasmic flow was by Weiss and Hiscoe in 1948.[13] They showed the normal streaming of axoplasm from the anterior horn cell down to the muscle fiber by placing a ligature on the nerve fiber and demonstrated damming up of axoplasm also distal to a ligature indicating a bidirectional flow of axoplasm. If the ligature is removed at this point, there is reestablishment of axoplasmic flow.

Quantitative analysis of slow axoplasmic flow was examined by Pleasure, using incorporated H_3-leucine into axonal protein in control peripheral nerve and nerve treated with acrylamide.[14] On the first day of an experiment, most of the radioactivity is at the point of injection in both sensory and motor axons. Subsequently, the radioactivity in control nerve begins to move along the axon and continues to move along day after day, whereas in the acrylamide treated peripheral nerve, there is no movement of the H_3-leucine incorporated protein. Here then is an elegant experiment showing interruption of slow axoplasmic flow by acrylamide which *in vivo* would be expressed as a severe polyneuropathy.

Thus there are two types of peripheral neuropathy. One type of neuropathy is a Schwann cell neuropathy of which post-infectious acute polyneuritis is a good example. Another class of neuropathy is an axonal dystrophy, and acrylamide-induced neuropathy is a prototype of that.

Finally, peripheral nerve disease can also be classified into disorders which are mainly motor or mainly sensory; and post-infectious acute neuritis is mainly a motor neuropathy, perhaps because there are different species of Schwann cells, one for the sensory axon and one for the motor axon, and the immunologic disease process is directed mainly against the Schwann cell associated with the motor axon. Other forms of peripheral nerve disease which are predominantly expressed as motor deficits include porphyria, Charcot-Marie-Tooth disease, chronic lead neuropathy, and diphtheritic neuropathy. Examples of neuropathies that are predominantly sensory in type are those of leprosy, vitamin deficiencies, diabetes mellitus, and arsenic poisoning.

In summary, the patient presented today best

represents post-infectious acute symmetrical polyneuritis. This is a syndrome of probable infectious origin. In view of the elevations in titer, it was produced perhaps by the Epstein-Barr virus in our patient. Subsequently, he went on to develop severe demyelination of motor axons perhaps due to a secondary immunologically based disorder directed at the Schwann cell associated with the motor axon.

REFERENCES

1. Landry O: Note sur la paralysie ascendante aigue. Gas hebd med chirurg 6:472-474, 1859
2. Guillain G: Radiculoneuritis with acellular hyperalbuminosis of the CSF. Arch Neurol Psych 36:975-990, 1936
3. Osler L, Sidell A: The Guillain-Barre syndrome. N Engl J Med 262:964-970, 1960
4. Heller G, DeJong R: The Guillain-Barre syndrome. Arch Neurol 8:179-193, 1963
5. Wiederholt W, Mulder D, Lambert E: The Landry-Barre-Strohl syndrome. Mayo Clin Proc 39:427-451, 1964
6. Matthews W, Howell D, Hughes R: Relapsing corticosteroid dependent polyneuritis. J Neurol Neurosurg Psychiatry 33:330-337, 1970
7. Asbury AK, Arnason B, Adams RD: The inflammatory lesion in idiopathic polyneuritis. Medicine 48:173-215, 1969
8. Rocklin R, Sheremata WA, Feldman RG: Guillain-Barre syndrome and multiple sclerosis. N Engl J Med 284:803-808, 1971
9. Arnason B, et al: Cell-mediated demyelination of peripheral nerve in tissue culture. Lab Invest 21:1-10, 1969
10. Ramos-Alvarez M, Bessudo L, Sabin AB: Paralytic syndromes associated with non-inflammatory cytoplasmic or nuclear neuronopathy. JAMA 207:1481-1492, 1969
11. Behan PO, Lowenstein L, Stilmant M, et al: The Landry-Guillain-Barre-Strohl syndrome and immune complex nephritis. Lancet 1:850-854, Apr 21, 1973
12. Calderon-Gonzales R, Rizzi H: Buckthorn polyneuropathy. N Engl J Med 277:69, 1967
13. Weiss P, Hiscoe H: Experiments on the mechanism of nerve growth. J Exp Zool 107:315-395, 1948
14. Pleasure DE, Mishler KC, Engel WK: Axonal transport of proteins in experimental neuropathies. Science 166:524, 1969

Medical Management and Prevention of Thromboembolism

Now we have a new approach to prophylaxis of venous thromboembolism, in addition to the oral anticoagulants . . . and that's low-dose heparin . . . The amount of heparin to achieve this is small and usually as little as 5,000 units, given subcutaneously so it gradually is absorbed every 8 to 12 hours. This will protect your patient from developing thromboembolism. It will not protect your patient who has an established thrombus from progressing. We're talking about prophylaxis, you see. Several studies have been conducted which have looked at the value of low-dose heparin, and the results are very encouraging. And in these studies, looking at patient populations with either minor surgery, more major surgery, quite major surgery, the trend is the same. The incidence of venous thrombosis is very high—between 25 to 45 percent, depending on usually the severity of the circumstance. And with low-dose heparin, the incidence is markedly reduced. The benefits seem not limited to major surgery; in a recent article, the workers compared the patients with myocardial infarction and surgical patients and essentially the benefit was similar—that is, from about a 20 percent incidence of venous thrombosis down to about 3 percent. In patients with major trauma, hip fracture or hip surgery, the protective effect of low-dose heparin seems less good. There is data that you will see within the coming months to suggest that even in this group, it provides reasonable protection, but not total protection, and it should not surprise us that the patient who has a tremendous provocation to thrombosis, with lots of tissue trauma, for example, is very different than one who has only the provocation of bed-rest without additional tissue trauma.

—Edward Genton, MD, *Denver*

Extracted from *Audio-Digest Family Practice*, Vol. 21, No. 37, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Refer to: Metabolic coma—Medical Staff Conference, University of California, San Francisco. West J Med 120:131-142, Feb 1974

Medical Staff Conference

Metabolic Coma

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *Our Medical Grand Rounds this morning will be concerned with the evaluation and treatment of the patient with metabolic coma. We have a case for presentation, and Dr. Clinton Lawrence will give the case summary.*

DR. LAWRENCE:† The case for today is that of a 29-year-old man with a history of psychiatric problems. Three days before he was admitted to Moffitt Hospital he ingested between 100 and 150 grains (6 to 9 grams) of ethchlorvynol. He was taken to a community hospital and upon arrival, approximately 35 minutes after ingestion, he was awake. Gastric lavage was done immediately and there was a good return of capsules and reddish material. Soon afterward he became apneic. An endotracheal tube was placed and he was transferred to the intensive care unit. There was no evidence of aspiration of stomach contents. He was kept in the unit for three days and during that time he was in stage IV coma. The blood ethchlorvynol level on admission there was 6.6 mg per 100 ml and results of a toxicologic screening were negative. Levarterenol drip of up to 32 micrograms per minute was necessary to maintain blood pressure of 70 to 80. Forced diuresis was attempted with furosemide and mannitol but urine output was less than 100 ml per hour. Metabolic acidosis was corrected with sodium bicarbonate. After three days the patient was transferred to Moffitt Hospital for hemodialysis in an attempt to end the need for pressors and maintain adequate perfusion. The patient was comatose on admission. Blood pressure was 70 to 90 while levarterenol was being given and was unobtainable when the drug was discontinued. The pulse rate was 90 and regular. There were no spontaneous respirations and ventilation was being carried out through the endotracheal tube. The patient was unresponsive to noxious stimuli, the pupils were mid-position and fixed, the fundi showed no papilledema, there was no reaction to caloric stimulation, and the extremities were flaccid and areflexic. There was no evidence of trauma. The hematocrit was 31 percent. Leukocytes numbered 7,000 per cu mm with normal differential of cells, and the platelet count was 265,000 per cu mm. Sodium content was 140 mEq, potassium 4.7 mEq, chloride 96 mEq and bicarbonate 24 millimols per liter. Blood urea nitrogen (BUN) was 26

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†E. Clinton Lawrence, MD, Intern in Medicine.

mg, creatinine 1 mg and calcium 8.4 per 100 ml. Studies of blood gases showed pH of 7.54, oxygen partial pressure (pO_2) of 92 mm and carbon dioxide partial pressure (pCO_2) of 28 mm of mercury with the patient receiving 30 percent oxygen.

A Schribner shunt was placed shortly after the patient was admitted to Moffitt Hospital and dialysis was carried out that evening in an attempt to end the need for pressor agents. Dialysis was done twice, for a total of ten hours, during the first 24 hours. Coincident with dialysis the blood pressure improved and levarterenol drip was discontinued.

In the nine days he has been in this hospital thus far—12 days after ingestion of ethchlorvynol —the patient is still comatose but there has been slow neurological improvement. He is unresponsive to pain, has a gag and swallow reflex in response to suctioning, and has spontaneous respirations of approximately 20 per minute. The pupils react briskly and reflexes are 2-plus without pathological reflexes. Hypotension is no longer a problem. At first 20 mg of furosemide approximately every three to five hours was necessary to maintain urine output of 3 liters a day, but now the output is satisfactory without the drug. The blood ethchlorvynol level at the time of admittance to the community hospital was 6.6 mg per 100 ml; on admittance to Moffitt it was 22 mg; the next day it was 27 mg and after ten hours of dialysis it was 22 mg. The most recent blood level, nine days after ingestion of the drug, was 11.5 mg.

Evaluation of Patients in Coma

Dr. Smith: *Thank you, Dr. Lawrence. We have asked Dr. Robert T. Scott to open the discussion concerning this patient, and also to speak on the general topic of the evaluation of patients with coma, particularly metabolic coma. I believe this is the first time that Dr. Scott has spoken at these exercises, so I will introduce him briefly. He was graduated from Harvard College and Harvard Medical School and then went for his medical internship and one year of residency in neurology at the University Hospital in Cleveland. He then returned to Boston to complete his training in neurology at the Massachusetts General Hospital. Following two years of service in the Air Force, he joined the faculty here in neurology two years ago and at present is Assistant Professor of Neurology and neurologist at the Detoxification Unit at San Francisco General Hospital, so he has had a lot of experience in cases such as the one we are considering here. We are pleased to have him with us to discuss this problem.*

Dr. Scott:* Thank you, Dr. Smith. The patient today presents most of the medical and neurological problems associated with profound coma due to ingestion of sedative-hypnotic drugs; and, since this is so common, I am going to spend most of my time this morning discussing the differential diagnosis of this particular type of coma, its characteristics, and, in particular, the means by which we can distinguish it from the structural lesions of the nervous system that mimic it.

I think that several points about this patient are worthy of note to begin with. First, despite gastric lavage, apnea occurred about an hour after the overdose. This emphasizes the fact that even an apparently successful lavage, with recovery of many pills, may lull us into feeling comfortable about the situation, whereas, in fact, the blood level from the drug already absorbed, is probably increasing. Fortunately, those caring for him were able to establish an airway without delay. Second, although, when admitted to the hospital, he was areflexic and had no pupillary responses or extraocular movements, these have returned during the past week. This indicates that this kind of coma is reversible, and that these neurological findings, ordinarily of the gravest concern when they develop in the course of cerebral hemorrhage or infarction, do not have the same significance in coma due to drugs.

I have examined the patient twice, several days after admission, and again a week later. On the first occasion, the pupils were reactive, but there were no extraocular movements to either doll's head maneuvers or caloric stimulation. Yesterday, the pupils had become briskly reactive and caloric responses were present but sluggish, but there were no movements to doll's head alone. I will discuss this rather common sequence of recovery of eye movements later on. An additional set of findings is of similar import. When I examined him yesterday, I could elicit no responses at all to deep painful stimulation. Despite this, however, reflexes were present, though somewhat asymmetrical, and he had bilateral sustained ankle clonus without Babinski signs, or, in fact, any response to plantar stimulation. What this means is that in drug-induced coma the neurological

*Robert T. Scott, MD, Assistant Professor of Neurology, and Neurologist at the Detoxification Unit at San Francisco General Hospital.

examination is commonly characterized by a dissociation of signs, such as ankle clonus in the absence of Babinski signs and by mild and occasionally more pronounced asymmetry of tone or reflexes in the limbs of one side as compared with the other.

To get to the subject of the coma itself, I want to begin by telling you some things that you already know. The word *coma,* for example, means simply sleep. In order to be conscious we need to have at least one functioning cerebral hemisphere to express that consciousness. Consciousness itself, though, is generated in the reticular activating system of the brainstem. It follows that unilateral lesions of one cerebral hemisphere, though they may produce aphasia or hemiplegia, do not cause coma unless there is involvement of the opposite hemisphere as well. Bilateral cerebral lesions commonly cause coma, but they do not necessarily do so; their size and location are important in this regard. The reticular activating system, located in the brainstem, is the generator, if you will, and the hemispheres are two light bulbs. If neither of the light bulbs is working, or if the generator is broken, the end result is coma. It is important for us to make the distinction between generator and light bulb dysfunction, because structural hemispheral lesions causing coma are often treatable, whereas those in the brainstem, because of their nature and inaccessibility, usually are not. Most drug-induced coma seems to be primarily the result of depression of the reticular activating system and only secondarily of the cerebral hemispheres. It has been shown experimentally that animals given depressant doses of barbiturates continue to have intact hemispheral function despite coma, while electrical activity in the reticular formation disappears relatively early.

What was done was to implant electrodes in the brainstem and in the cerebral cortex, and then stimulate peripheral sensory nerves. Ordinarily in waking animals, this produces changes in electrical activity in both sites, but in animals given barbiturates, the responses could still be found in the cortex long after those in the brainstem had disappeared. We will see later on how this selective depression of brainstem function can help us to tell drug induced from other kinds of coma. The reticular formation is schematically outlined in Figure 1. This figure is not entirely accurate

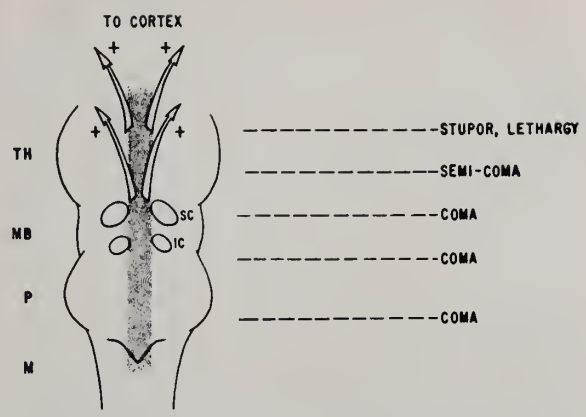


Figure 1.—Schema of reticular formation. From Chapter 1, The Comatose Patient, **In** Sharpe JC, Marx FW Jr (Eds): Management of Medical Emergencies, 2nd Ed. McGraw-Hill Book Co., 1969. Reproduced with permission from the editors and the publishing company.

because it shows the reticular formation as a narrow road running through the pons and upper brainstem to the thalamus and then to the limbic system of the frontal and temporal lobes and eventually to the cerebral hemispheres. In fact, it is a rather wide highway network with multiple side roads connecting with the cranial nerve nuclei and respiratory and cardiovascular centers of the brainstem. Suffice to say for now that it is a very important structure in the maintenance of the waking state and that it appears to be selectively depressed in drug induced coma.

To return to the practical problem at hand, I want to give you a basis on which to think, with regard to probabilities, about patients in coma. Table 1 is taken from the excellent monograph by Plum and Posner[1] and represents the final diagnosis in a series of 386 cases admitted to hospital with the initial diagnosis of coma of undiagnosed cause. Note that of these patients the vast majority (216) had diffuse cerebral disorders for which metabolic and toxic causes were most frequent. Only 69 patients had supratentorial mass lesions; and of the 386 patients, only 37 had lesions that could be treated surgically, such as subdural hematoma, abscess, or tumor. Exogenous toxins as illustrated by the patient presented today, and endogenous toxins (uremia, hepatic coma, etc.) are the largest group, constituting nearly one half of all these cases of coma, exogenous toxins accounting for more than one-quarter of them. Thus, you can see that statistically the odds are on metabolic coma; the problem is how this information can be profitably applied to a given patient.

TABLE 1.—*Final Diagnosis in 386 Patients with "Coma of Unknown Etiology"**

1. Supratentorial Mass Lesions	
Epidural hematoma	2
Subdural hematoma	21
Intracerebral hematoma	33
Cerebral infarct	5
Brain tumor	5
Brain abscess	3
Total	69
2. Subtentorial Lesions	
Brainstem infarct	37
Brainstem tumor	2
Brainstem hemorrhage	7
Cerebral hemorrhage	4
Cerebellar abscess	2
Total	52
3. Metabolic and Diffuse Cerebral Disorders	
Anoxia or ischemia	51
Concussion and postictal states	9
Infection (meningitis and encephalitis)	11
Subarachnoid hemorrhage	10
Exogenous toxins	99
Endogenous toxins and deficiencies	81
Total	261
4. Psychiatric Disorders	4

*From Plum F, Posner JB: The Diagnosis of Stupor and Coma, Philadelphia, F. A. Davis, 2nd edition, 1972 (reference No. 1) (Reproduced with permission from the author and publishing company)

The Importance of the History

What is the approach to the patient in coma? I wish to emphasize that for me the single most important item, and paradoxically the one most commonly neglected, is the history of onset of the alteration of consciousness. The physical examination, as we will find, can be of great help, and laboratory data are obviously important. We will concentrate now on the physical examination and the clues which it can provide as to the cause of coma, not because it is the best way, but because practically it is usually all that can be done in many patients. I have found that the most common mistake in diagnosing comatose patients is that the history is not searched vigorously enough. Instead, after intravenous glucose, thiamine, and naloxone hydrochloride have been given, we send off every available fluid to the laboratory and then sit on our hands. The problem is that many drugs are difficult to detect even in ideal circumstances, and, more practically, that toxicology laboratories are not accessible everywhere, nor are they able to do immediate analyses at any time of the day or night. Frequently results come back days later and have little effect on what actually happens to the patient. My own approach is to work hard on the history, and then to weigh carefully that information in light of the physical examination.

What, then, should we look for in the history, and how do we go about getting it? Let us begin with *how*. I make the assumption, which usually turns out to be correct, that everyone, no matter how down and out, has someone in this world who really cares about him. If you find that person—and it may be mother, brother, landlord, bartender, or drinking buddy—you can usually find out three things. First, what the patient's spirits have been lately; second, whether or not he is a drug abuser and, if so, what kind he uses; and third, what the circumstances of his sickness were. Was he found in bed with empty tranquilizer bottles at his side, or were there signs of a struggle in his room? Was there vomitus about; had he been incontinent of urine? Had he been hit on the head or been in a fight in the last several months? Sometimes people who know the patient may be quite unable to supply this kind of information; but, particularly if the onset of coma was on the street or in a store or in a bar, a call to the ambulance driver, police, or owner of the store may give you valuable information. Did the patient have a seizure before he became unconscious, or did he complain of severe headache? Let me illustrate with an example of a patient who was recently treated on the neurology service at the San Francisco General Hospital. He was a 45-year-old man brought to the hospital by the police from jail because of bizarre behavior during the course of which he had driven his car across a median strip and smashed into several others. On examination, he was hallucinating and was very agitated and disoriented. He looked like a patient in delirium tremens and was treated as such. Laboratory work showed no abnormality, yet the sensorium did not clear after several days of treatment with sedation and restraints. His wife, too timid at first to bring it to the attention of the house staff, finally asked them if taking Miles Nervine® (which contains large amounts of bromides) could cause a person to act like this. Serum bromides were found to be in the toxic range, and the patient slowly recovered over a period of weeks. In this case the diagnosis would have been missed had the wife not volunteered the information. The same thing happens every day. Direct questioning about drug use could have established the diagnosis at the time of admission.

TABLE 2.—*Approach to Patients in Coma*

Observe:
1. Position, spontaneous movements, alertness
2. Respirations (Rate, Depth, Pattern)
   Normal—any level
   Cheyne-Stokes—bihemispheral
   Central Neurogenic Hyperventilation—mid pons, acidosis
   Ataxic—low pons, medulla
   Short-cycle Cheyne-Stokes—low pons, medulla
3. Eye Movements
4. Pupils

What, then, should be asked? The most important question concerns the mode of onset. Drug coma may come on over a period of half an hour or an hour, as in the patient presented today; it does not happen within seconds or minutes except in the case of intravenous opiate or barbiturate overdose. Very sudden onset of coma suggests embolic cerebral infarction, subarachnoid or intracerebral hemorrhage, or seizure. Gradual onset, over hours, is consistent with drug ingestion, carotid occlusion, intracerebral hemorrhage, hypoglycemia or hepatic coma. Subacute onset over days or weeks is suggestive of brain abscess, subdural hematoma, brain tumor, or the cumulative effect of large amounts of sedative drugs or anticonvulsants. None of these classifications is ironclad, but to think in these terms is exceedingly useful in narrowing down the broad range of possibilities. For example, if a patient known to have been depressed has been taking tranquilizers or abusing drugs, that helps us a bit. But it does not mean that he does not have a subdural hematoma. If he is found in his room with vomitus on the bathroom floor, and the place in disarray, one would still be reluctant, despite other evidence suggesting it, to diagnose metabolic coma. Vomiting may, of course, be caused by drugs, but more commonly, in our experience, is an accompaniment of suddenly raised intracranial pressure, as might occur in subarachnoid or intracerebral hemorrhage or acute epidural or subdural hematoma. I would like to emphasize finally that metabolic coma is potentially reversible coma; what we really want to do is to maintain blood pressure, and respiration until these functions recover spontaneously.

The Physical Examination

Next I want to direct your attention to the other part of the equation—the physical examination. Even in ideal circumstances it is often the only early source of information. I want to admit at the outset that the examination of the comatose patient is not easy. It is not easy even for a neurologist in many cases. Coma represents perhaps the most difficult neurological condition to evaluate because we are unable to rely on the active participation of the patient, his waking perceptions, verbal responses, and so forth. Simple schemes for examining coma only in terms of various neurological signs are often over simplified, and thus not really accurate. Complicated schemes you will forget. At any rate I want to tell you some of the things that have been helpful to me in looking at patients in coma (Table 2). The very first thing is so simple that it is usually overlooked, and that is just to look at the patient. *Look!* Observe him without pinching, poking, or shouting. Look at his position in bed. Does he move both arms and legs spontaneously, or move around restlessly in bed? If arm and leg movements are symmetrical, it reassures me that a significant hemiparesis is not present. If the patient blinks, yawns, or attends to sounds in the room, the level of coma is not deep. Get the *gestalt* of how the patient feels to you; think of the contrast between the agitation and motor hyperactivity of a patient with uncal herniation compared with the calm serenity of a patient with drug ingestion or other metabolic coma.

Then look at the respirations and listen to them. It is worthwhile to measure their rate and to assess their depth and regularity. But before doing this, be sure that the airway is clear. If it is obstructed, abnormalities may be produced which may mimic neurological dysfunction. Normal respirations may occur in coma produced by lesions at nearly any level in the nervous system, so that it is not necessarily true that all patients with upper midbrain lesions will have the same breathing pattern. Cheyne-Stokes respirations, for example, are commonly thought to be a sign of serious central nervous system disease; in actuality, they are usually benign, and, while they may occur in bihemispheral coma, or upper midbrain lesions, they are not uncommon in congestive heart failure or in older patients in general. Central neurogenic hyperventilation—marked by sustained, very deep, rapid, regular respirations with a pronounced expiratory accentuation—can occur in lesions of the mid-pons, but also in severe systemic acidosis, meningitis, acidosis of the cerebrospinal fluid, and upper airway obstruction or other pulmonary dysfuncion. Ataxic respirations, with irregular

rate and chaotic variations in the depth and duration of inspiration, are signs of severe impairment of the function of the respiratory center in the low pons and medulla and are associated with a poor prognosis. So-called short-cycle Cheyne-Stokes respirations are not gentle and regular like the classic Cheyne-Stokes and imply low pontine trouble.

The Extraocular Movements—and, Last, the Pupils

After the respirations, the next things to assess are the extraocular movements and then the pupils. You may be jolted by the fact that I have put the examination of the pupils *last* whereas you may be used to thinking of them first. As a general rule, they are of very little value by themselves and are so often confusing that, aside from a few circumstances which I shall discuss later, it seems best to relinquish the emphasis that is commonly placed on their size and reactions. The problem in a nutshell is that most people look at the pupils and follow them, without paying enough attention to other things that are most apt to be of value in following a patient in coma.

This brings us to the next point, and that is that coma is hard work and requires great patience. If you are in a hurry, you had better get someone else to handle the case for you. It takes a lot of work for the person who is taking care of the patient—though it is very easy for the neurologist to say get this, order that, and so on. I realize that and acknowledge it, but neither I nor any other neurologist invented coma; it is simply one of those things that we have to put up with, whether we like it or not. It is more comfortable to like it, and it can be a lot of fun to find out from small clues here and there something that, had you not done the work, would not otherwise have been suspected.

The Level of Consciousness

To get back to the patient again, let us look at how we can assess and follow the most important part of the neurological evaluation of the patient in coma—the level of consciousness. The first problem is the terminology—words like *coma, stupor,* and so on have as many meanings as there are people in this room, so that like *big* or *small* they are only very general terms. The lightest form of impairment of consciousness—that is, drowsiness or sleepiness—is characterized by the ease with which a patient can be aroused to full alertness, often by gently speaking his name or tickling his skin. In light stupor, you may have to pinch or shout to arouse the patient, and, in deeper stages of coma, repeated deep pinching may be necessary. And in our patient today even this produced no discernible change in his level of unconsciousness. Because these terms are so vague, I suggest that you describe what the patient does in response to all of the stimuli that you apply, and what he does spontaneously, instead of saying that he is in "stage II coma," or is "semicomatose" or "stuporous." It is best to stimulate the patient to a maximum level of alertness, which may require vigorous pinching, in order to use this response as a baseline.

You will find that especially in metabolic coma, though in other types as well, patients vary from minute to minute in their level of spontaneous alertness and that for this reason your examination may be totally different from that of another equally competent examiner done only 15 or 20 minutes later. Obviously, in order to avoid incorrect conclusions, for example that the patient is in deeper coma than before, you want to make sure that he has had adequate stimulation when you assess him on each occasion. Commonly one reads in charts that the patient "responds to pain"; clearly this "response to pain" has to be qualified in order to have meaning. Decorticate posturing in response to painful stimulation or simply, as in deep coma, a change in the rate of breathing, is far different from a groan, a shout, or active attempts to push away your stimulating fingers.

Incidentally, two additional aspects are worthy of mention. First, pinprick as a means of producing pain is limited to patients who are awake or in a very light coma; in deeper coma, it is not an adequate stimulus (the area of skin stimulated by the pin point is too small) and it has the disadvantage of making holes in the skin which bleed. Second, it is wisest not to discuss comatose patients in their presence in terms other than those that you would use if they were wide awake. They may well hear, understand, and remember what you have said, particularly if you think that they are deeper in coma than is actually the case.

Before discussing eye movements and the clues they provide us in examining patients in coma, I want to spend some time on the pupils, their size and reactions to light. The main control over pupil

size in the normal state is largely parasympathetic, and arises in the Edinger-Westphal nucleus in the third or oculomotor nuclear complex. The afferent part of the reflex arc consists of the retinal receptors, optic nerve and tract. The efferent arc travels with the third nerve to innervate the ciliary ganglion. If all these structures are intact, pupils respond to light by constricting. As a general rule, pupils in most types of metabolic or toxic coma, with a few exceptions, react to light; in our patient today, they did not, even to very bright light at several different times. How can we explain this fact on the basis of the information I have just given you? There seems to be no adequate explanation other than to say that some part of the mechanism was depressed by the drug involved, most probably part of the Edinger-Westphal nucleus in the upper brainstem, since conduction in nerve fibers seems more resistant to the effect of sedative-hypnotic drugs than conduction across synapses. There certainly is adequate evidence of failure of function of many other parts of the brainstem in this patient in that his respirations and blood pressure required external support.

Bilateral smallness of pupils is seen in many situations. This occurs in normal sleep and in the apneic phase of Cheyne-Stokes respiration, and is the hallmark of pontine hemorrhage or infarction. In poisoning, it is indicative of opiate, propoxyphene hydrochloride, or organic phosphate intoxication. In all these circumstances, the pupils react, though the reaction may be slight. Argyll-Robertson pupils differ from the previous type of small pupils in that they do not react to light, and are usually asymmetrical and irregular in shape. Smallness of pupils occurs *unilaterally* in Horner's syndrome, which may be associated with or antedate the illness producing coma.

A common problem is to decide in the presence of pupillary inequality if one is larger than normal or if the other is smaller. Often this must be done in the context of other neurological signs. Most frequently the house staff becomes concerned over minor degrees of anisocoria in comatose patients; in this situation it is better to look for other evidence, as we will discuss later, of neurological dysfunction in terms of hemiparesis or third nerve palsy than to spend too much time worrying about the pupils. At times old photographs or the recollection of a relative may reassure us that an observed pupillary inequality is old. Horner's syndrome in coma is strongly suggestive of a thalamic hemorrhage which has compressed the subthalamic pathways arising in the hypothalamus that supply sympathetic pupil-dilating impulses.

Bilateral largeness of pupils is most commonly seen in anoxic-ischemic episodes, such as cardiorespiratory arrest, but bilateral destruction of the third nerve or nucleus as in uncal herniation can do the same thing, as can pharmacological agents, such as glutethimide, atropine or atropine-like drugs. When the largeness is unilateral, it is worrisome because it implies that uncal herniation is occurring. I want to emphasize, though, that you will not see unilateral dilatation due to uncal herniation in the absence of hemiparesis, usually severe, and impairment of consciousness. It follows that if you see a patient on the ward with such a pupillary inequality, it is more likely that someone has dilated one eye with a mydriatic agent or that he has existing ocular disease, such as uveitis, which may have bound down the iris fibers with synechiae so that it does not constrict properly. Adie's syndrome should be mentioned for the sake of completeness because it can produce unilateral or bilateral enlargement which responds so sluggishly to light that the reaction may be imperceptible. It is commonly seen in young people and is often associated with absence of knee and ankle jerks.

Doll's Head and Caloric Stimulation Responses

At this point I want to tell you a little about eye movements in coma, their significance, and how to examine them. Much of this is probably familiar to you, but there is some problem with the terminology. The phenomenon of conjugate movement of the eyes in relation to the head which occurs with passive head rotation in patients in coma is called doll's head, or, if you will, the oculocephalic response. The way the examination is done is to hold the lids open, rotate the head from side to side or up and down, and observe the extent of both horizontal and vertical eye movements. I want to emphasize that this is not a passive phenomenon; it is not as though the eyes are floating on a sea of air in their sockets, and simply stay put by inertia when the head is rotated. It is, on the contrary, the result of polysynaptic reflex activity in many parts of the brain-

stem, whose afferent impulses arise in the neck muscles and are transmitted to the extraocular muscle nuclei by the median longitudinal fasciculus. Doll's head responses cannot be elicited in waking normal patients because our cerebral cortex is able to override the reflex. In coma due to bilateral cerebral cortical lesions, the normal ability to suppress the reflex is lost, and the eyes move when the head is rotated. In patients with coma due to lesions of the brainstem, however, the movements will be absent because of interruption of the brainstem circuits required for their production.

The oculovestibular response, another brainstem reflex, uses stimulation of the semicircular canals by cold water irrigation, often called *caloric stimulation,* to accomplish the same thing. In patients whose coma is due to bilateral or diffuse cerebral cortical dysfunction, irrigation of one external auditory canal with cold water results in tonic deviation of the eyes *toward the ear irrigated.* This is a confusing point because it is seemingly just the opposite of what happens in awake, normal persons. Many of you recall the *COWS* mnemonic—cold opposite, warm same, but *this applies only to the direction of the fast phase of nystagmus* produced in normal awake persons. What happens in coma is that this nystagmus disappears and only the reflex tonic deviation remains.

Which test should be performed and when? Since their purpose is to examine movements of the eyes in patients who are unresponsive, it should be apparent that if the patient has full voluntary eye movements and is awake, or if he has full roving side-to-side movements in coma, they are unnecessary. If the eyes do not move side to side spontaneously, either doll's head or caloric testing can be done. Since the head rotation may need to be quite vigorous, it is preferable not to perform doll's head maneuvers in patients suspected of cervical spine injury because of the danger of cord damage. On the other hand, for caloric testing the ear canals and drums must be intact. As a rule, patients in coma tend to lose doll's head before caloric responses. From what we have said previously, it should be obvious that since neither response is seen in patients who are awake, either may be used as a diagnostic test in suspected psychogenic or feigned coma; nystagmus, in place of tonic deviation, will be seen following caloric testing, and the doll's head phenomenon will not be seen when the head is rotated.

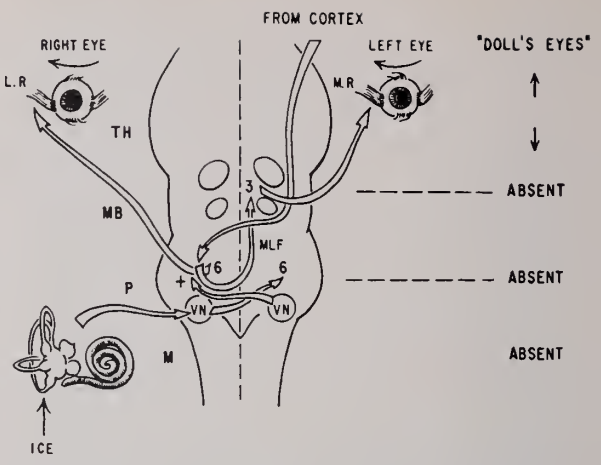


Figure 2.—From Chapter 1, The Comatose Patient, **In** Sharpe JC, Marx FW Jr (Eds): Management of Medical Emergencies, 2nd Ed. McGraw-Hill Book Co., 1969. Reproduced with permission from the editors and the publishing company.

What the Responses Tell

Of what value is the information obtained from these maneuvers? Figure 2 shows the upper pons and midbrain, the median longitudinal fasciculus, and the extraocular muscle nuclei which it connects with one another, as well as the vestibular nuclei. A lesion at any place along these pathways may alter the doll's head or caloric responses. For example, with a lesion of the right third nerve or nucleus, the eyes will move conjugately to the right if the head is rotated to the left or if the right ear is irrigated with cold water. When the head is rotated to the right, or the left ear is stimulated with cold water, the left eye will deviate to the left, but the right eye will not move medially, and if the head is passively moved up and down, the right eye will not show vertical movements. All these movements are innervated by the right third nerve. If there is damage to the left sixth nerve, the left eye will not move laterally when the head is rotated to the right or when the left ear has cold water instilled in it. All other eye movements will be normal. In patients in coma, the importance of testing extracular movements lies in the fact that their presence tells us about the function of much of the brainstem. Fisher[2] has formulated this "rule of the eyes" as follows: *Full horizontal excursions of both eyes, whether they occur spontaneously as in roving eye movements, or to doll's head or caloric stimulation, indicate that the pons and midbrain are relatively normal and exclude brainstem lesions below the third nerve nucleus as a cause of coma.* Now this is true with one

TABLE 3.—*Classification of Coma by Presence or Absence of Eye Movements*

	Structural	*Metabolic*	*Toxic*
1. Coma with full eye movements on doll's head maneuver or caloric stimulation (at rest eyes may diverge, rove, or conjugately deviate)	Supratentorial Hemispheral (Infarct, tumor, hemorrhage, etc.)	Anoxia (unless terminal) Hepatic Coma Uremia CO_2 Narcosis Hyponatremia Hypo/Hyperglycemia Postictal Septic Shock Hypo/Hypercalcemia	Ethanol Phenothiazines Opiates Tricyclics Atropine
2. Coma with absence of eye movements (doll's head or calorics)	Brainstem or Pontine (Infarct, hemorrhage, tumor, or bilateral compression from herniation)	Wernicke's	Sedative-Hypnotics Curare, Succinylcholine General Anesthesia Dilantin Mysoline

proviso; that is, that intoxication with sedative hypnotic drugs can be excluded. What occurs with them will be discussed later.

The main point that I want to leave you with today is that, depending on these eye movements, we can break down causes of coma into two large groups, one with full eye movements, and the other with absence or impairment of eye movements. It is a very useful classification because most patients in metabolic coma, with the exception of sedative hypnotic overdose, have full eye movements (Table 3). In coma with full extraocular movements, the eyes may diverge as in normal sleep, or they may rove from side to side, or they may be conjugately deviated to one side or the other. If they rove fully from one side to the other there is no reason to do caloric or doll's head testing, because by their presence these spontaneous movements have given you the information already; but if they are conjugately deviated to one side, or do not rove, then further testing is needed. With lesions of a cerebral hemisphere which are accompanied by conjugate deviation of the eyes toward the side of the lesion, caloric irrigation of the ear opposite the side of the lesion will produce slow conjugate deviation of the eyes away from their original position. If this does not occur, a brainstem lesion in the pontine gaze center near the abducens nucleus may be responsible. The rule is that hemispheral lesions, in the absence of brainstem compression from herniation, are associated with full eye movements to either doll's head or caloric tests. Metabolic causes of coma due to endogenous toxins, such as uremia, hepatic coma, anoxia, or hypoglycemia, are accompanied by full eye movements.

Ethanol intoxication, unless other sedative drugs are present as well, does not fix the eye movements, nor do phenothiazines, opiates, tricyclic antidepressants or atropine-like drugs.

Let us now turn to coma in which eye movements are impaired. Initially, as the eye movements disappear, and this is most clearly apparent in the stages of progressive stupor seen in sedative intoxication, the doll's head responses are the first to go, followed later by the responses to caloric testing, which seems a stronger stimulus. Some structural lesions of the pons or brainstem are associated with absent eye movements. These include pontine hemorrhage, infarction or tumor, as well as bilateral compression of the brainstem from uncal or central herniation. In lesions confined to the pons, the pupils will be small and reactive to light, presumably because parasympathetic impulses can still be transmitted via the Edinger-Westphal nucleus more rostral in the midbrain. When a pontine lesion extends upward, as is commonly seen in the late stages of pontine hemorrhage destroying this area, the pupils become large. Similarly, the pupils enlarge, one before the other, in cases of uncal herniation. It is very important to think of Wernicke's disease in a drowsy or stuporous patient whose eyes do not move properly. This is clearly a neurological emergency because in these patients, unless treated promptly with intravenous thiamine, irreparable damage to midbrain and thalamic structures with severe and permanent memory impairment may develop, especially if intravenous glucose is administered without thiamine.

The major cause of absence of eye movements

in coma is intoxication with sedative hypnotic drugs. These include all the barbiturates, the benzodiazephines, general anesthesia with almost any agent, and anticonvulsants. Neuromuscular blocking drugs like curare fix eye movements but do not, of course, cause coma. Why do they affect the eye movements? This is really the crux of what we are saying today, and the reason is not completely clear. Two ways of explaining the phenomenon are that sedative drugs are known to exert particular depression of polysynaptic, as opposed to monosynaptic (like the tendon jerks) reflexes, and the pathways governing eye movements are clearly polysynaptic. Furthermore, we know that these drugs selectively depress the reticular formation, also polysynaptic, which lies directly adjacent to the eye muscle nuclei in the brainstem and upper pons. Whether these drugs are concentrated to a greater extent here than in other areas of the nervous system is not certain.

Since drugs and structural lesions both can produce coma with absence of eye movements, how do we distinguish them? How can we differentiate a mass lesion which has stopped extraocular movements by compressing the brainstem from a toxic drug like ethchlorvynol which produces the same effect? It is not easy and sometimes the question must be resolved by arteriography or other special procedures. Nevertheless, there are clinically useful guidelines, the foremost being the history. Without that, our patient for today would probably have had a cerebral angiogram; you can imagine the difficulty in doing this kind of procedure in the face of hypotension and respiratory failure, and it is fortunate that it was not necessary. In physical examination, we look for grossly asymmetrical signs in structural lesions, such as progressive hemiparesis leading to hemiplegia, unilateral decerebrate or decorticate posturing, unilateral ophthalmoplegia preceding bilateral loss of eye movements, and progressive loss of consciousness during a period of observation. Another helpful clue lies in the respiratory pattern. Patients with mass lesions causing progressive obtundation tend to have labored and irregular respirations, and this is also the case with pontine lesions, such as a hemorrhagic mass. In contrast, the respirations in drug coma are easier, initially like those of normal sleep, then gradually failing without ataxic breathing, central neurogenic hyperventilation, or apneustic respirations. They often cease entirely without any dramatic warning. This is one reason that close observation of patients is coma is essential.

In general, patients with metabolic or drug coma have symmetrical neurological signs, but this is not always the case, particularly if there is a pre-existing minor neurological deficit which, as you are aware, may become dramatically more noticeable in these circumstances. Another rule that may prove helpful is that *structural lesions of the central nervous system do not cause systemic arterial hypotension;* in fact, the opposite is more apt to be found, whereas hypotension is not uncommon in severe sedative hypnotic overdose. It should be borne in mind that a ruptured spleen is hard to diagnose in post-traumatic coma.

Neurological Effects of Sedative Hypnotic Drugs

Because the subject of this talk is really coma due to drug ingestion, I want to review with you the neurological events that follow ingestion of a sedative hypnotic drug. Many patients, when seen soon after ingestion of the drug, are not in coma, but have unmistakable signs to indicate the cause of their progressive lethargy. We are often confronted with the situation in which a patient is brought to the emergency ward drowsy, confused or slightly obtunded without apparent explanation. Since many of them may be intoxicated with barbiturates, benzodiazepines or other sedative drugs, it is worth knowing how to make the diagnosis. The first effects are on mental alertness, and if the patient is unknown to us the decrease in alertness may be so subtle as to escape detection. With progressive intoxication, however, certain rather stereotyped findings appear in speech, eye movements, and coordination. These patients have slurred dysarthria, much like that due to cerebellar disease or intoxication with alcohol. At this time, they almost always have nystagmus, which, however, may not be appreciated unless they are asked to shift visual fixation rapidly from one side to another. Even small therapeutic doses of the benzodiazepines, given in the course of withdrawal from alcohol, produce this finding. This earliest objective sign of intoxication is often missed, because proper testing is not carried out. Horizontal nystagmus is more common and appears earlier than vertical nystagmus, and, because drugs are the most common cause of nystagmus, the combination of these two types of nystagmus usually indicates sedative hypnotic drug intoxi-

cation. Fine movements of the limbs are ataxic, as is the gait, and many patients demonstrate asterixis. In coma, they may be any stage from light drowsiness to deep coma, and their eye movements are invariably fixed. If eye movements are normal, the diagnosis of coma due to sedative hypnotic overdose is almost certainly incorrect, as is illustrated by the following case.

A 54-year-old woman was brought to the hospital after being found in her hotel room unresponsive. It was learned from her family that she had been depressed for some time, and that she had been taking phenobarbital for insomnia and nervousness and a diuretic for hypertension. She was last seen, and appeared normal, the day before she was brought to the hospital. On admission she was mildly hypertensive, in deep coma arousable to making bilateral limb movements only with deep pinch, had very brisk reflexes with bilateral extensor plantar responses, and had full eye movements to doll's head maneuvers. The diagnosis of coma due to phenobarbital overdose was made and the patient was admitted to the respiratory intensive care unit. When a lumbar puncture was performed ten hours after admission because of fever, bloody xanthochromic spinal fluid was obtained under increased pressure.

Comment: In this hypertensive, depressed woman, two statistically likely causes of coma are drug overdose and intracerebral hemorrhage. The presence of intact doll's head movements made it impossible for her to have the former, which had been diagnosed solely because of the history of depression and use of the drug. With further history from her daughter it was learned that the patient was discovered in a pool of vomitus in the bathroom. Later, at autopsy a ruptured berry aneurysm with massive subarachnoid hemorrhage was found.

During recovery from coma caused by sedative hypnotic drugs, one will observe a lightening of the level of consciousness, restitution of respiratory function, reappearance of tendon reflexes and return of eye movements. There is no definite sequence, however, in this recovery; some patients recover eye movements early, and others may have fixed eyes when they are able to make high level complex movements of the limbs in response to stimulation. Again we emphasize that this dissociation of selective effects on the nervous system is characteristic. Eye movements to caloric stimulation almost always return before doll's head maneuvers can elicit them, and it is not unusual to see during the course of return of eye movements an apparent third nerve palsy which may be unilateral or bilateral and which may simulate internuclear ophthalmoplegia in which one eye moves laterally with nystagmus on attempted conjugate gaze, but the other does not move medially. Tone and reflexes are variable during intoxication and recovery, and may change drastically over the course of minutes, with clonus one minute and flaccidity the next. It is likely that these changes in tone, reflexes and level of responsiveness are due to phasic alterations in the generating activity of the reticular formation, somewhat analogous to the changes in its activity during the normal waking state, which encompasses total alertness, as well as drowsiness and somnolence in alteration. The pupils may also participate in this variability in responsiveness, and be reactive and midsize at one moment and smaller or larger only minutes later. In general, with recovery, pupillary reactions return relatively early, and many patients never have alterations of pupillary light reflexes even in very deep coma.

Summary

To summarize what we have discussed this morning, I want to stress that the approach to the diagnosis of coma must be at many levels, with each bit of data analyzed for agreement with the others. The history, physical examination and toxicological laboratory data must fit with each other; none alone can do the job adequately. In the initial physical examination and in subsequent examinations, the most important single indicator of the state of the patient is the level of consciousness. Sequential examinations should stress the maximum alertness as measured by what the patient does when stimulated, and this should be clearly indicated in the chart so that others may be able to follow observable responses and not generalities like "semi-coma," "stupor," and the like when they are asked to see the patient. Finally, the simple observation of eye movements can help to separate large groups of causes of coma from each other, and help us to avoid fruitless and possibly hazardous diagnostic tests. If all the tests do not help to make the diagnosis, I have found it very useful to sit down with family and any others who have had close contact with the patient and *take the history again,* stressing possible head injury, drug use, exposure to toxins, or

TABLE 4.—*A Guide to the First Examination of a Comatose Patient*

1. Do not just do something, stand there (and get the history)
2. Give 50 percent dextrose *after* specimen for blood sugar is drawn
3. Do not attribute coma in alcoholics to ethanol
4. Do make sure airway is adequate early
5. Get both blood *and* urine for toxicology screen
6. Do not forget the skull films
7. Mild focal signs are common in metabolic coma, but dense hemiplegia is not
8. If in doubt, squirt
9. Lumbar puncture early, if any suspicion of meningitis, otherwise best to wait awhile. Cerebrospinal fluid should be normal

progressive personality changes that may indicate an unsuspected brain tumor or other intracranial mass lesion.

In closing, I wish to leave you with a few general remarks which constitute what I have found to be major common problems encountered in treating these patients (Table 4).

• When seeing a patient in coma for the first time, a worthwhile rule is, "Don't just do something, stand there." Frequently patients are brought to the emergency ward in coma alive and breathing, only to get into trouble when roughly handled. If respirations are not adequate, it is far easier to give manual assistance with a bag or insert a nasopharyngeal airway than to try immediately to insert an endotracheal tube, with the potential risk of airway obstruction from laryngospasm or inability to pass the tube. When patients have cardiorespiratory arrest on arrival at the hospital after they have breathed on their own for possibly hours in coma at home, we should ask ourselves *why*.

• Give 50 percent glucose solution only after a specimen for blood sugar determination has been drawn and, in the case of suspected meningitis, after spinal fluid has been obtained. The reason is that if hypoglycemia is the cause of coma, full evaluation is needed and requires knowledge of the actual level of blood glucose and because many patients with intracranial mass lesions become more responsive because of the osmotic effect of hypertonic glucose. Without an initial blood glucose, a patient may erroneously be assumed to have been hypoglycemic.

• In alcoholics, the diagnosis of coma due to ethanol ingestion is almost always incorrect. When coma is present in these patients, it should be assumed to be from another cause until proved otherwise. The "odor of alcohol (which is practically odorless in fact) on the breath" has cooked the goose of more than one patient with subdural hematoma.

• When a toxicology screen is indicated, remember to send specimens of blood and urine and, if available, gastric contents. Many alkaloid drugs, such as opiates and belladonna derivatives, are not present in the blood in quantities large enough to be measured, but are present in urine, and in cases of poisoning the largest concentrations of the drug involved are found in the stomach.

• Get skull films and look at them; they do no one any good in the file room.

• Do not diagnose metabolic or drug coma in the presence of dense hemiplegia.

• Do not do routine lumbar puncture immediately in comatose patients, unless there is a suspicion of meningitis from the history or examination. It is better to wait and look at the skull films for evidence of increased pressure (erosion of posterior clinoids) or pineal shift, and to look carefully at the fundi for papilledema. This is not to minimize the importance of the spinal fluid examination, but rather to emphasize that lumbar puncture may precipitate neurological deterioration in patients with raised intracranial pressure. The spinal fluid in patients in metabolic or drug coma should be normal in all respects, save for low or high sugar content in hypo and hyperglycemia respectively. Occasionally patients with myxedema or hypercalcemia may have moderate elevations of protein content. There should be no more than three to five mononuclear cells per high power field in normal spinal fluid or in fluid from patients in metabolic or drug coma.

• If the patient does not improve or worsens and the clinical course is not consistent with your initial diagnosis, consider the possibility that the diagnosis is incorrect. The batting average of an experienced neurologist approaches 90 percent but we are often wrong and should always be in doubt.

• The final rule is: If in doubt, squirt. In the diagnosis of subdural hematoma, you have heard the old dictum that a cupful of dye is worth a roomful of neurologists. It is still true.

REFERENCES

1. Plum F, Posner JB: The Diagnosis of Stupor and Coma, 2nd Ed. Philadelphia, F. A. Davis, 1972
2. Fisher CM: The neurological examination of the comatose patient. Acta Neurologica Scandinavica, supplemental 36, vol 45, 1969

Important Advances in Clinical Medicine

Epitomes of Progress—Radiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Radiology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Radiology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities
California Medical Association, 731 Market St., San Francisco, CA 94103

The Present Status of Retrograde Cholangio-Pancreatography

RETROGRADE CHOLANGIO-PANCREATOGRAPHY is a valuable new diagnostic technique for the radiographic diagnosis of diseases of the biliary tree and pancreas. With the development of the side-viewing fiberoptic duodenoscope, it is possible to cannulate the ampulla of Vater under direct vision through the endoscope and to inject radiographic contrast material retrograde into the pancreatic duct or the common bile duct. In this way radiographs showing the pancreatic ducts and its branches can be made, whereas before such pancreatograms were possible only intra-operatively. Tortuosity, stricture, dilitation, obstruction and calculi in the main duct or its branches are findings in chronic pancreatitis, while carcinoma of the pancreas may cause displacement, narrowing or obstruction of the duct. Cannulation of the common bile duct permits opacification of the biliary tree in the presence of impaired liver function and biliary tract obstruction. Gallstones, tumors and strictures of the common duct can be diagnosed when duct obstruction renders radiographic visualization by intravenous cholangiography impossible, and without the risk of bile peritonitis or hemorrhage associated with transhepatic cholangiography.

The technique is currently in a phase of enthusiastic evaluation, typical of all new diagnostic modalities, in which the indications, complications and diagnostic value are being defined. The difficulty of the cannulation should not be underestimated. Despite the fact that several endoscopists report a high success rate, most series indicate that failures are numerous until expertness is obtained. The cost of the examination is extremely high, as it takes from thirty minutes to two hours of both an endoscopist's and a radiologist's time, it occu-

pies a fluoroscopy room for the same period, and it requires an investment in a side-viewing endoscope that has little other use. The appropriate instrument with accessories costs as much as $10,000. So far, the risk to the patient appears to be minimal. A few patients have mild abdominal pain and fever after the examination. Elevation of the serum amylase, sometimes to high levels, is noted regularly. The first case of fatal necrotizing pancreatitis following the procedure was reported recently. Infection of pancreatic pseudocysts may occur.

Answers are being sought to the questions of how many endoscopists should take the time to acquire the expertise necessary to perform the cannulation, which and how many patients should have the study, and what the significance of the radiographic findings is. Finally, it must be determined if the results sufficiently alter therapy and diminish morbidity and mortality to justify the cost and risk to the patient and the expenditure of the physician's time.

ROBERT N. BERK, MD

REFERENCES

Kasugai T, Kuno N, Kobayashi S, et al: Endoscopic pancreatocholangiography. Gastroenterology 63:217-226, Aug 1972

Morrissey JF: To cannulate or not to cannulate (Editorial). Gastroenterology 63:351-352, Aug 1972

Cotton PB: Cannulation of the papilla of Vater by endoscopy and retrograde cholangiopancreatography—A progress report. Gut 13:1014-1025, 1972

Ammann RW, Deyhle P, Butikofer E: Fatal necrotizing pancreatitis after peroral cholangiopancreatography. Gastroenterology 64:320-323, 1973

Ingelfinger FJ: Endoscopic pancreatocholangiography: Progress and problem (Editorial). N Engl J Med 287:879-880, Oct 26, 1972

Osteomyelitis in Drug Addicts

HEMATOGENOUS OSTEOMYELITIS, predominantly spondylitis, is an increasingly frequent complication of intravenous drug abuse. The bacteria causing these infections are unusual, consisting largely of Pseudomonas aeruginosa or Klebsiella aerobacter. Because of the destructive nature of these pyogenic infections, it is essential to establish the diagnosis immediately and to determine the causative organism in order to institute appropriate therapy.

Any patient with a history of intravenous drug abuse with localized skeletal pain should be suspected of having osteomyelitis, although early radiographs are often normal. Frequently, radioactive isotope bone scans which reflect increased osteoblastic activity will be positive before bone destruction can be detected on routine radiographs. Needle aspiration or bone biopsy will often yield the specific organism for sensitivity studies; however, this may require multiple attempts.

Between 1969 and 1971, 32 cases of skeletal infection in drug abuse patients were diagnosed at Los Angeles County-University of Southern California Medical Center. Sixty-six percent of the cases involved the spine or sacroiliac joint and 18 percent involved the area around the wrist or sternoclavicular joint. The radiographic findings in these areas were indistinguishable from tuberculosis, and, in fact, this form of osteomyelitis was seen ten times more frequently than tuberculosis.

Delays (averaging two months) in diagnosis and treatment occurred for the following reasons: (1) Lack of awareness of the association of intravenous drug abuse and osteomyelitis; (2) dismissal of patients as normal when radiographs were normal, without requesting bone scans; (3) positive radiographs frequently attributed to tuberculosis; (4) treatment of patients with Gram positive or broad spectrum antibiotics without bacteriological confirmation.

Successful therapy was accomplished when specific antibiotic therapy utilizing gentamicin or a combination of gentamicin and carbenicillin was instituted.

DANIEL M. KIDO, MD
D. M. FORRESTER, MD

REFERENCES

Kido D, Bryan D, Halpern M: Hematogenous osteomyelitis in drug addicts. Am J Roentgenol Radium Ther Nucl Med 118:356-363, 1973

Holzman RS, Bishko G: Osteomyelitis and heroin addicts. Ann Intern Med 75:693-696, Nov 1971

Lewis R, Gorback S, Altner P: Spinal pseudomonas chondroosteomyelitis in heroin users. N Engl J Med 286:1303, June 15, 1972

Echocardiography and the Radiologist

OFTEN THE RADIOLOGIST is consulted by the clinician as to the cause of cardiomegaly initially diagnosed on radiographic examination of the chest. In many instances the history is of no help, there are no previous films for comparison, the electrocardiogram findings are equivocal and the patient's illness so acute that treatment must be begun promptly.

The armamentarium of the radiologist, until recently, included two types of examination: radioisotope studies and CO_2 infusion into the right atrium. These were mainly designed to exclude

the presence of pericardial fluid, but had definite limitations. The former technique requires 500 ml of fluid for positive identification and the latter specifies the absence of fluid in the right pleural space. Both examinations must be performed by experienced personnel within their respective departments, and the patient must be transported to the equipment.

The advent of improved techniques in diagnostic ultrasound eliminates the need of several of the above requirements; now the equipment is easily transported to the patient's bedside, the amount of pericardial fluid that can be reliably detected is in the range of 100 to 200 ml, and the presence of pleural fluid is not a factor.

There are additional benefits derived from the echocardiographic examination, and much more information than merely the presence or absence of pericardial fluid is available. These additional data include mitral valve function, cardiac chamber size, myocardial dimensions, contractile physiology, estimation of stroke volume, ejection fractions, intracardiac tumors, and dyskinetic segments of the posterior left ventricular wall.

The equipment is relatively inexpensive and the technique when utilized by a trained radiologist is non-traumatic and a valuable tool in cardiac diagnosis.

ROBERT L. WILSON, MD

REFERENCES

Feigenbaum H: Echocardiography. Philadelphia, Lea & Febiger, 1972

Feigenbaum H: Clinical applications of echocardiography. Prog Cardiovasc Dis 14:531-558, May 1972

Renal Function Following Double Dose Infusion Intravenous Cholangiography

A STUDY OF TEN PATIENTS following intravenous infusion of 40 ml of iodipamide methylglucamine diluted with normal saline solution to 100 ml, administered in a half-hour period, resulted in an increase in uric acid clearance and a decrease in free water clearance. There were no changes in clearance of inulin, paraminohippuric acid, osmoles, urine pH or calculated renal blood flow. Opacification of the biliary ducts was above average in eight of the ten patients studied.

The changes in renal function after slow infusion of iodipamide methylglucamine were not associated with any discernible deleterious effect. However, the combination of increasing uric acid excretion rate plus increasing urinary concentration would seem to increase the potential for uric acid nephropathy.

Consequently, it would be advisable to hydrate the patient before intravenous cholangiography. Since the rapidity of injection may have other hemodynamic effects, including an increase in kidney size, changes in plasma volume and a reduction in renal blood flow, it also appears safer to use a slow infusion technique.

E. NICHOLAS SARGENT, MD

REFERENCE

Sargent EN, Barbour BH, Espinosa N: Evaluation of renal function following double dose infusion intravenous cholangiography. Am J Roentgenol Radium Ther Nucl Med 117:412-417, 1973

Noninvasive Radionuclide Myocardiography with Radioactive Potassium

THE COMBINATION of exercise stress testing with precordial scanning after intravenous injection of radioactive potassium provides a new approach to noninvasive evaluation of regional myocardial perfusion.

Conventional coronary arteriography demonstrates the location and extent of obstruction in the coronary vasculature. Direct injection of radionuclides into the coronary arteries gives further information about blood flow across stenotic coronary arteries and the perfusion of the myocardium distal to obstruction. However, this procedure also requires cardiac catheterization with its attendant risks.

The intravenous injection of radioisotopes of potassium, cesium, and rubidium and also radioiodinated fatty acids has been used in precordial imaging to successfully demonstrate regions of transmural scar. Currently, potassium-43 is the radionuclide of choice. Exercise stress compromises the perfusion of the vascular bed supplied by stenotic major coronary arteries or collateral vessels. Its addition to the procedure of noninvasive imaging allows delineation of the areas of perfusion deficit in patients with coronary atherosclerosis resulting in angina pectoris rather than infarct.

M. E. MORTON, MD, PH D

REFERENCE

Zaret BL, Strauss HW, Martin ND, et al: Noninvasive regional myocardial perfusion with radioactive potassium. N Engl J Med 288:809-812, Apr 19, 1973

Pulmonary Radiographic Findings in Cystic Fibrosis in Adults

CYSTIC FIBROSIS in adults is no longer a rarity, not only because of advances in therapy which prolong life but also because less typical or severe cases can now be diagnosed with the aid of improved tests. In the past, in adults with the disease the diagnosis had been made at a later age than the average for all cases. In the future, however, the best prognosis may be found in patients diagnosed in the first few months of life, with or without symptoms; a recent study projected that three-fourths of such children would survive to the age of 20. It is of note that in two-thirds of adult cases the patients are men, and that the least affected adults are also usually men.

Radiographic findings in young adults with cystic fibrosis reflect the fact that all degrees of severity may be found in this age group. In the worst cases, the radiographs have all the findings of a typical childhood case: nodular shadows from mucus impaction or pus-filled bronchi, parallel line and ring shadows from bronchiectasis (predominantly cylindrical), soft parenchymal densities from focal pneumonia, and well-demarcated opacifications due to lobar, segmental, or focal atelectasis. Lung volume is increased, though not all patients have an increased anteroposterior diameter. Pathologically, however, destructive emphysema is minimal. The heart is usually narrow in diameter and vertical in position, with prominence of the right ventricular outflow tract on the lateral projection; the hila are prominent because of pulmonary hypertension, lymphadenopathy from chronic infection, and the surrounding radiolucency of over-expanded lungs.

Non-radiologists often use the term *fibrosis* to describe some of the linear or irregular markings in this disease, but real fibrosis is found only after unusually severe infections; most of these markings actually represent chronically infected airways and atelectasis. Characteristically, the bronchiectasis of cystic fibrosis differs from that of most other non-tuberculous causes in that it is most evident in the upper lobes. Similar findings may be found in patients with recurrent pulmonary infection due to immune deficiency or unknown cause. The upper lobe distribution is particularly striking in adults with less severe cystic fibrosis, effectively mimicking tuberculosis with sub-apical irregular nodular densities and segmental or upper lobar atelectasis. The mildest cases show only some degree of pulmonary over-expansion; other abnormal markings may be evident only during episodes of active infection.

The diagnosis of cystic fibrosis should be suggested whenever a young adult—often with a history of "asthma" or bronchitis or recurrent pneumonia— has radiographic evidence of chronic airway obstruction and infection, especially with bronchiectasis sparing the lung bases.

PAUL J. FRIEDMAN, MD

REFERENCES

Shwachman H, Redmond A, Khaw KT: Studies in cystic fibrosis: Report of 130 patients diagnosed under 3 months of age over a 20-year period. Pediatr 46:335-343, 1970

Shwachman H, Kulczycki LL, Khaw KT: Studies in cystic fibrosis: A report of 65 patients over 17 years of age. Pediatr 36: 689-699, 1965

Tomashefski JF, Christoforidis AJ, Abdullah AK: Cystic fibrosis in young adults: An overlooked diagnosis, with emphasis on pulmonary function and radiological patterns. Chest 57:28-36, 1970

Analgesic Nephropathy: The Radiologist's Role in Diagnosis

RENAL DISEASE caused by the abuse of analgesic drugs, so-called analgesic nephropathy, is partially reversible and therefore important to diagnose early. It was formerly believed that phenacetin alone caused the disease, but the most recent evidence suggests that phenacetin may not be the only cause. In combination with other analgesics it produces renal damage, but there is evidence to suggest that aspirin alone in large doses, particularly associated with a decreased fluid intake, can cause identical damage.

The patients typically are neurotic women in the 30 to 60 year age group with a long history of vague back or abdominal pain or headaches, weakness and anemia. They often have had urograms because of urinary tract infection or unexplained pyuria.

In the early stages of the disease there is an interstitial nephritis and microscopic foci of papillary necrosis. At this time it is not possible to make the diagnosis from the x-ray studies although there may be some diminished concentration of contrast material in the collecting system. When the disease has progressed to radiographically visible areas of medullary necrosis or total papillary necrosis, the diagnosis should be suggested if sickle cell disease, diabetes, or obstruction with infection can be excluded.

The alert radiologist can be the first physician to elicit the telltale history by exploring in depth

the patient's analgesic intake over the previous ten years. Sometimes it is necessary to obtain this history from a friend or relative, since the patients rarely are honest regarding their intake of analgesic drugs.

Since urinary infection is a common secondary phenomenon in patients with analgesic nephropathy, it is important not to mistake the urographic findings for those of pyelonephritis. Patients have been misdiagnosed as having "chronic pyelonephritis" because of this association. When a club-shaped calyx is found in the presence of a smooth renal outline, papillary necrosis rather than atrophic pyelonephritis should be diagnosed. Occasionally sloughed papillae will remain *in situ* and calcify, appearing as typical ring-shaped calcifications on the plain film.

LEE B. TALNER, MD

REFERENCES

Abel JA: Analgesic nephropathy—A review of the literature, 1967-1970. Clin Pharmacol Ther 12:583-598, Jul-Aug 1971

Lindval N: Renal papillary necrosis—A roentgenographic study of 155 cases. Acta Radiol, suppl 192:1, 1960

Hare W: Scientific exhibit, First Asian Oceanian Congress of Radiology. Melbourne, Australia, Nov 1971

A Diagnostic Approach to Renal Mass Lesions

RECENT EXPERIENCE here and abroad shows that percutaneous puncture is a reliable means of diagnosing simple renal cysts. Exploratory operations for diagnostic purposes should be necessary in rare instances only. For the radiologist the problem has become one of selecting from all patients with renal masses those who are suitable for puncture—that is, those who are likely to have renal cysts. Although nephrotomography and angiography are accurate most of the time, neither is 100 percent diagnostic since avascular tumors may mimic renal cysts.

Ultrasonic B-scanning has become a reliable means of determining whether a renal mass is solid, cystic, or mixed. The streamlined work-up of a patient with renal cyst consists of the following steps: (1) establish the *presence* of a renal mass by urography or tomography or both, (2) establish the fluid-filled nature of the lesion by ultrasound, and (3) cyst puncture. With this approach, most patients with renal cysts need not have multiple view nephrotomography and arteriography. In lesions where the echo is indeterminate, mixed or solid, angiography is performed and the decision as to puncture or to operate can then be made.

After aspirating a portion of the cyst fluid for diagnostic purposes, water-soluble contrast medium is injected and cyst filming is carried out to assure that the cyst punctured accounts for the entire mass demonstrated on the urogram. The diagnosis of tumor within a cyst is made on the basis of the findings in the aspirated fluid and may or may not be corroborated by the renal cystograms.

When the fluid aspirated from a cyst contains new or old blood and all the analyses of the fluid fail to demonstrate signs of malignancy and the cystogram is normal, the subsequent management may be open to debate. Although approximately 75 percent of these hemorrhagic cysts will prove to be benign, the experience with this type of lesion is too limited at present and, in good risk patients, surgical exploration is advisable to rule out tumor.

LEE B. TALNER, MD

REFERENCES

Asher WM, Leopold GR: A streamlined diagnostic approach to renal mass lesions with renal echogram. J Urol 108:205-208, Aug 1972

Jeans WD, Penry JB, Roylance J: Renal puncture. Clin Radiol 23:298-311, Jul 1972

Increased Sensitivity of 99mTc-Diphosphonate Over Radiography in Skeletal Imaging for Metastases

OSTEOBLASTIC LESIONS are perceived in conventional radiography only when the calcium concentration exceeds normal by at least 30 percent. The dense appearance of these lesions may persist even after clinically favorable response to therapy. Nuclear medical imaging, on the other hand, is not only more sensitive in detection, but also shows changes in the accumulation rate of radioactivity in the lesions reflecting success of the therapy.

The sensitivity of radioisotope techniques results from accelerated ionic exchange of the radionuclide with the crystal of bone in the lesions as compared with non-involved skeletal structures. Ethane-hydroxy diphosphonate labeled with technetium-99m is the currently preferred agent for radionuclide imaging of skeletal metastases. This localizes in the calcium hydroxy-apatite crystal of bone by chemisorption. Strontium-85 and strontium-87m exchange with the calcium of the crys-

tal. The more expensive cyclotron-produced fluorine-18 exchanges with the hydroxyl ion of the crystal.

Clinical studies show imaging with 99mTc-diphosphonate to be the most effective method for locating skeletal metastatic lesions. The use of the technetium-99m label results in decided improvement of resolution and overall image quality. In one series of 60 metastatic lesions, all were demonstrated by 99mTc-diphosphonate, while only 56 percent could be detected with 18F. Radiographic visualization was obtained in only 28 percent.

Both radionuclide and radiographic studies may be used when there are symptoms or laboratory evidence suggesting osseous metastasis, but the bone scan with 99mTc-diphosphonate is by far the more sensitive tool in discovering bone neoplasm and following the course of therapy.

M. E. Morton, MD, PH D

REFERENCES

Silberstein EB, Saenger EL, Tofe A, et al: Imaging of bone metastases with 99mTc-Sn-EHDP (diphosphonate), 18F and skeletal radiography—A comparison of sensitivity. Radiol 107: 551-555, Jun 1973

Pendergrass HP, Pottsaid MS, Castronovo FP Jr: The clinical use of 99mTc-diphosphonate (HEDSPA)—A new agent for skeletal imaging. Radiol 107:557-562, Jun 1973

The Importance of Recognition of Gastric Bezoars after Operation for Ulcer

Over the years it has become apparent that patients who have undergone Bilroth I and II procedures, either with or without vagotomy, have been noted to have masses presenting in the fundus of the stomach, even though they have been fasting for one or more days. On occasion this mass has been confused with a tumor and operation done on that account.

In the event that this was recognized as a bezoar there have been some initial attempts at surgical removal rather than the initial treatment of choice, which is to break up these soft food bezoars with gastroscopic instruments, followed by maintenance therapy with proteolytic enzymes. Following this, many of these patients can be controlled by dietary means alone.

Edward R. Dana, MD

REFERENCES

Goldstein HM, Cohen LE, Hagen R, et al: A frequent complication in the postoperative ulcer patient. Radiol 107:341-344, May 1973

Buchholz RR, Haisten AS: Phytobezoars following gastric surgery for duodenal ulcer. Surg Clin North Am 52:341-352, Apr 1972

One Method of Detecting Early Gastric Cancer by X-ray Examination

Because of the very high rate of gastric cancer in Japan, a method of detection of early lesions utilizing air-releasing granules, simethicone, and a double-contrast air and barium method of examination has been devised.

Through this method, cancers have been detected which are so small as to defy gastroscopic visualization. Operation on early lesions has yielded a cure rate approaching 90 percent.

The Japanese technique requires considerable practice and good patient cooperation, as well as good spot filming equipment. Because of the low rate of gastric cancer in this country and the high incidence of peptic disease, this method is not likely to replace conventional methods of examination, but certainly may supplement them in certain circumstances.

Scott-Harden, reviewing six years of experience with a double contrast technique in the general radiology department of Cumberland Infirmary, Carlisle, found it "most encouraging" in that it stood up well to endoscopic check. Such a method might be more simply adapted to routine practice.

Edward R. Dana, MD

REFERENCES

Obata WG: A double-contrast technique for examination of the stomach using barium sulfate with simethicone. Am J Roentgenol Radium Ther Nucl Med 115:275-280, Jun 1972

Kawai K, Takada H, Takekoshi T, et al: Double contrast radiograph on routine examination of stomach. Am J Gastroenterol 53:147-153, 1970

Scott-Harden WG: Evaluation of double contrast, gastro-duodenal radiology. Br J Radiol 46:153, Feb 1973

Opportunistic Pulmonary Infections

The immunologically compromised host—for example, patients on immunosuppressive regimens after organ transplantation, or receiving steroids, or who have advanced malignant disease—is subject to a wide variety of "opportunistic" pulmonary infections, often caused by unusual infectious agents. The etiological agent must be identified as early as possible for prompt administration of appropriate therapy, since pulmonary infections in such patients progress rapidly and not infrequently result in death. The radiographic appearance of such opportunistic infection, although not specific or pathognomonic, can suggest "categories of infectious agents" to guide appropriate diagnostic endeavor or therapy pending results of cul-

tures. In addition, percutaneous pulmonary aspiration with fluoroscopic guidance is a procedure of reasonably high yield when other conventional attempts at establishing the identity of the causative organism, including transtracheal aspiration, are unproductive.

RONALD A. CASTELLINO, MD

REFERENCES

Blank N, Castellino RA, Shah V: Radiographic aspects of pulmonary infection in patients with altered immunity. Radiol Clin North Am 10:175-190, Apr 1973

Bandt PD, Blank N, Castellino RA: Needle diagnosis of pneumonitis. JAMA 220:1578-1580, Jun 19, 1972

Bragg DG, Janis B: The radiographic presentation of pulmonary opportunistic inflammatory disease. Radiol Clin North Am 11: 357-369, Aug 1973

Endocrine Tumors Localized by Catheter Venous Sampling

PRIMARY ALDOSTERONISM may be due to an aldosterone-secreting tumor (aldosteronoma) or bilateral adrenal hyperplasia. Selective adrenal venography, although capable of visualizing small aldosteronomas with an accuracy of 70 to 80 percent, is accompanied by the hazard of adrenal hemorrhage. However, determination of aldosterone levels in peripheral and adrenal vein blood (obtained via selective adrenal vein catheterization) provides more accurate information regarding the presence or absence of an aldosteronoma versus bilateral hyperplasia, as well as correct lateralization of an aldosteronoma. Small test injections required to determine accurate cathether placement during venous sampling are fluoroscopically monitored and should eliminate the hazard of adrenal gland damage.

In patients with hyperparathyroidism a similar approach—venous sampling for hormone-level determination—can be utilized for more accurate localization of the abnormal parathyroid tissue. This technique is particularly useful in patients with persistent symptoms who have had previous operation on the neck for hyperparathyroidism. Multiple vein specimens are drawn from jugular, innominate, and as many thyroid veins as possible via a catheter introduced into a femoral vein.

RONALD A. CASTELLINO, MD

REFERENCES

Kahn PC, Kelleher MD, Egdahl RH, et al: Adrenal arteriography and venography in primary aldosteronism. Radiol 101:71-78, Oct 1971

Horton R, Finck E: Diagnosis and localization in primary aldosteronism. Ann Intern Med 76:885-890, Jun 1972

Doppman JL, Wells SA, Shimkin PM, et al: Parathyroid localization by angiographic techniques in patients with previous neck surgery. Br J Radiol 46:403-418, Jun 1973

Detection of Relapse of Hodgkin's Disease by Routine Radiographs

THE *routine* UTILIZATION of chest and abdominal radiographs for detection of relapse in patients with Hodgkin's disease was recently assessed. Of 442 patients treated for cure between 1955 and 1970, 130 had relapse. The diagnosis of relapse was initiated by radiographic findings alone in 35 percent of the 130, by simultaneous radiographic and clinical evidence in 30 percent, and by clinical evidence alone in 35 percent. The surveillance radiographs (the abdominal film primarily used to detect changes in retroperitoneal lymph nodes previously opacified by lymphography) yielded positive findings equally between abnormalities of mediastinum-lung and retroperitoneal lymph nodes. Careful comparison of current radiographs with multiple previous studies is essential for detection of the nuances of change indicative of relapse. Periodic surveillance radiographs are essential in the post-therapy evaluation of patients with Hodgkin's disease.

RONALD A. CASTELLINO, MD

REFERENCE

Castellino RA, Blank N, Cassady JR, et al: Roentgenologic aspects of Hodgkin's disease—II. Role of routine radiographs in detecting initial relapse. Cancer 31:316-323, Feb 1973

Intracranial Aneurysms in Children

IT IS BECOMING APPARENT that cerebral aneurysms occur more commonly in children than was previously believed. These aneurysms are usually large—a surprising finding in light of the pathogenic theory that the weakened bifurcation point gradually balloons. Unexpectedly, they occur most commonly at the internal carotid bifurcation.

Pediatricians and neurologists have traditionally treated children with subarachnoid hemorrhage conservatively. Cerebral angiography has been sidestepped or needlessly postponed because the procedure was feared unsafe. However, experience with selective percutaneous femorocerebral catheter angiography using appropriately-sized catheter matcrials has shown the method to be perfectly safe, even for neonates. Its facility provides complete visualization of the cerebral circulation, an absolute necessity in the demonstration of aneurysms.

In a pediatric hospital of constant size, only 11 childhood aneurysms were diagnosed in 20 years

preceding the era of routine femorocerebral catheter angiography. In only two years, the same number were discovered once routine angiography was instituted for evaluating subarachnoid hemorrhages. In the same two-year period, 38 arteriovenous malformations were identified, most of them after angiography was used less hesitantly.

JOSEPH R. THOMPSON, MD

REFERENCES

Thompson JR, Harwood-Nash DC, Fitz CR: Cerebral aneurysms in children. Am J Roentgenol Radium Ther Nucl Med 118:162-175, 1973

Patel AN, Richardson AE: Ruptured intracranial aneurysms in the first two decades of life—A study of 58 patients. J Neurosurg 35:571-576, Nov 1971

Tantalum, A New Contrast Agent for Tracheobronchography

DURING THE LAST FIVE YEARS there has been an ongoing evaluation of powdered tantalum as a contrast agent for tracheobronchography. A nasotracheal catheter is passed, under local anesthesia, and its tip positioned in the lobar or segmental bronchus of the area to be opacified. The tantalum is insufflated from a powder blower with compressed air.

Tantalum is a heavy metal with a density of about 16, and it has a number of properties that make it an improved contrast agent. It is nonirritating to the lungs, it adheres to the mucous blanket—thus coating the airways without occluding them; and the material does not cause sensitivity reactions as iodine-containing compounds sometimes do. Because of its extreme density and the obviation of a suspensory medium, only 3 to 4 ml of tantalum are required for opacification of the bronchial tree. This compares with 20 to 40 ml when the usual contrast agents are employed. Tantalum can thus be used in the neonatal period and in patients with diminished respiratory reserve. Experimental studies of mucocillary clearance from the airways are also possible.

There are, however, some drawbacks to the insufflation of a particulate material. In patients with excessive secretions in the airways, adequate dispersion of the powder and opacification of all airways may not be achieved. Tantalum, as with most unoxidized fine particulates, will burn under appropriate conditions; hence the generator system must be grounded, and air, not oxygen, must be used for insufflation. Flow rates of 0.2 to 0.5 liters per second are required for insufflation; care must be taken, therefore, to insure the catheter is never wedged into a small bronchus.

Powdered tantalum for tracheobronchography is still an experimental drug under FDA control and is not available for general use. The most apparent present use is for opacifying the larger central airways. Work is in progress on an inhalation system which may overcome some of the problems of insufflation.

GORDON GAMSU, MD

REFERENCES

Nadel JA, Wolfe WG, Graf PD, et al: Powdered tantalum—A new contrast medium for roentgenographic examination of human airways. N Engl J Med 283:281-286, Aug 6, 1970

Gamsu G, Nadel JA: New technique for roentgenographic study of airways and lungs using powdered tantalum. Cancer 30:1353-1357, 1972

Gamsu G, Platzker A, Gregory G, et al: Powdered tantalum as a contrast agent for tracheobronchography in the pediatric patient. Radiol 107:151-157, 1973

Gamsu G, Weintraub RM, Nadel JA: Clearance of tantalum from airways of different caliber in man. Am Rev Resp Dis 107:214-224, 1973

New Concepts in the Management of Mycosis Fungoides

MYCOSIS FUNGOIDES is a rare form of malignant lymphoma that initially is confined to the skin but eventually progresses to involve extracutaneous sites such as lymph nodes, spleen, liver, lung, bone marrow and other organs. Although when untreated the disease is considered fatal, it seems that adequate treatment when delivered early in the natural course of the disease may offer cure to some patients. In a recent review of 132 mycosis fungoides patients treated by total skin irradiation with 2.5 MeV electrons, it was reported that 14 became disease-free for intervals varying from three to fourteen years following a single course of treatment, and to date none of these patients has had relapse. It seems reasonable to believe that these patients initially had disease limited to the skin and that it was cured by the treatment with electrons.

Long-term remissions (two to four years) have also been achieved by total body topical applications of dilute aqueous solutions of nitrogen mustard. Use of this treatment method has been complicated by the fact that hypersensitivity reactions to the drug develop in about 40 percent of patients. Furthermore, in order to sustain remission when obtained, permanent maintenance therapy was required. In spite of these obvious disadvantages, topical application of nitrogen

mustard seems to be a potent method for the control of cutaneous mycosis fungoides, but its curative potential is yet to be established. At present, it seems justifiable to say that all patients with mycosis fungoides confined to the skin should be treated as early as possible with electron beam irradiation.

When extracutaneous spread occurs, prognosis seems extremely poor, and most patients die within one year despite treatment efforts with various chemotherapeutic agents. However, in some patients it seems possible to diagnose a premalignant state in the lymph nodes. In those patients physical examination reveals abnormal lymphadenopathy, with benign changes of "dermatopathic lymphadenitis" observed on histological examination. Actuarial analysis of survival of patients with generalized plaque involvement of the skin shows that 67 percent of patients who presented with no lymphadenopathy before irradiation survived five to ten years, compared with 43 percent of those who had enlargement of lymph nodes when first seen. Only one of twenty-six patients with no initial lymphadenopathy eventually had extracutaneous dissemination, compared with ten of twenty-eight who had nodal enlargement at the outset. It seems possible to state that mycosis fungoides patients who have dermatopathic lymphadenitis constitute a high risk group for subsequent extracutaneous dissemination. Improvement of the prognosis of advanced mycosis fungoides will require the introduction of methods for early diagnosis of premalignant and malignant extracutaneous involvement, as well as the establishment of new philosophies of treatment. Clinical trials designed to explore such new diagnostic and treatment methods are in progress.

Zvi Fuks, MD
Malcolm A. Bagshaw, MD
Eugene M. Farber, MD

REFERENCES

Fuks ZY, Bagshaw MA, Farber EM: Prognostic signs and the management of mycosis fungoides. Cancer: In press

Van Scott EJ, Kalmanson JD: Complete remission of mycosis fungoides lymphoma induced by topical nitrogen mustard (HN_2)—Control of delayed hypersensitivity to HN_2 by desensitization and by induction of specific immunological tolerance. Cancer 32:18-29, Jul 1973

ADVISORY PANEL TO THE SECTION ON RADIOLOGY

Robert H. Reid, MD, *Chairman, Los Gatos*
Chairman, CMA Section on Radiology

Duane E. Blickenstaff, MD
CMA Section on Radiology, Secretary
La Jolla

Frederick Sondheimer, MD
CMA Section on Radiology
Assistant Secretary
San Francisco

Vernon R. Gee, MD
CMA Scientific Board
Redding

Melvin P. Judkins, MD
Loma Linda University

Ronald A. Castellino, MD
Stanford University

Antolin Raventos, MD
University of California, Davis

Elliott Lasser, MD
University of California, San Diego

Gabriel Wilson, MD
University of California, Los Angeles

Bernard J. O'Loughlin, MD
University of California, Irvine
California College of Medicine

A. R. Margulis, MD
University of California, San Francisco

E. Nicholas Sargent, MD
University of Southern California
Los Angeles

John C. Bennett, MD
San Francisco

EDITORIAL

The Unconscious Patient

THE MEDICAL STAFF CONFERENCE on Metabolic Coma that appears in this issue draws helpful attention to the diagnosis and treatment of a problem that looms large for almost any physician engaged actively in the care of patients. Protection of the integrity of the brain rates top priority among medical goals, and the presence of impaired consciousness from any cause necessarily means that a substantial proportion of the brain's function already is depressed or damaged. To use a medical analogy, stupor or coma reflects brain failure and the necessity for prompt neurological action just as dyspnea and frothy sputum reflect heart failure and the necessity for prompt cardiological action.

Human consciousness with all its psychological richness and subtlety depends on the close functional interaction between the cerebral cortex of the two hemispheres on the one hand, and a diffuse network of nerve cells centrally distributed along the upper brain stem and called the reticular formation on the other.[1] The gradual loss of either side of this functional pair leads to wakeful dementia while the abrupt impairment of either member produces sleep-like stupor or coma. Sleep-like though the appearance may be, however, coma and natural sleep are very different neurological states, a point well illustrated by the fact that cerebral metabolism remains normal during sleep[2] but is invariably reduced in stupor or coma.[3]

When the physician meets patients with impaired consciousness, the immediately compelling questions about the cause are, Is it structural or metabolic? Is there one lesion or many? What must I do immediately? and, Can it be specifically treated? Remarkably, the general answers to these questions can often be gained from close attention to a relatively few clinical details. In his discussion at the Staff Conference, Dr. Scott has properly emphasized how much one learns from a little extra effort in history taking. My emphasis will be on the physical examination, but in either case the point is that careful clinical thinking yields more important information that a scatter-shot of hurried laboratory tests.

Although the individual causes of stupor and coma are many,[3] they all fall into one of four categories: Structural lesions are almost always supratentorial or subtentorial in locus, rarely both, while metabolic disorders tend to affect the brain at several different levels at the same time. Psychogenic unresponsiveness or pseudocoma is known by its remarkable freedom from neurophysiological abnormality.

Supratentorial structural lesions impair consciousness mainly by their size; as they enlarge they squeeze the brain downward on the diencephalon. This impairs the rostral reticular formation and adds a bilateral physiological abnormality to whatever local pathological effect the hemispheres have undergone from the primary lesion. Most patients with supratentorial lesions causing stupor have physical signs that imply a combination of focal hemispheric troubles (for example, aphasia and sensory-motor hemiparesis), plus diffuse abnormalities (such as impaired consciousness, yawning, small pupils, bilateral increased muscular resistance and bilateral extensor plantar responses). An important negative finding with supratentorial lesions is that until the terminal stages of illness there are no signs that indicate the brain stem is directly impaired; pupillary and oculovestibular responses remain intact and the respiration and circulation are never depressed.

Subtentorial structural lesions cause stupor or coma only if they damage or compress the centrally placed reticular formation of the mid-brain or upper pons. Rapidly expanding cerebellar masses can occasionally do this by displacing the brain stem upward, but the commonest subtentorial cause of coma is an infarct or hemorrhage of the central brain stem. The clinical signs are characteristic because the reticular formation lies immediately on top of or interspersed with, respectively, the ocular motor nuclei, the median longitudinal fasciculus, the vestibular nuclei, and the

respiratory centers. Damage the reticular formation, therefore, and one necessarily damages at least some of these other structures too, so that pupillary, oculovestibular and respiratory abnormalities are present from the beginning and point directly to a lesion in the stem. Often, but not always, the brain stem lesions lie more to one side than the other, so that one finds asymmetrical signs of neurological abnormality in the stem itself combined with asymmetrical long tract motor abnormalities below that point.

Metabolic encephalopathy is by far the commonest cause of unconsciousness in general hospitals. Clinically, most patients with metabolic coma appear to have more depression of forebrain than of brain stem. However, the striking and diagnostic finding with most metabolic agents is that they selectively depress certain susceptible functions at several different levels of the brain but at the same time spare other functions which equally depend on structures at those self-same levels. Obviously, no mechanical lesion could at one and the same time possess this combination of launching both a diffuse and a selective attack. There are other helpful clues: most metabolic encephalopathies cause delirium in advance of stupor or coma and many of them are accompanied by various forms of tremor or myoclonus in their pre-coma stage. Almost all metabolic comas spare the pupillary light reflex (the examining physician must use a bright light and beware of overlooking a brisk response) and many of them spare or even enhance oculovestibular responses as well. Respiratory changes are common with metabolic coma, often because the disease itself produces acid-base changes. Although the metabolic encephalopathies occasionally may produce asymmetrical signs, they usually do not and they never impair central sensory pathways except as a part of the overall depression of consciousness.

Psychogenic unresponsiveness can externally copy organic coma, but the clinical fine points give it away. The diagnostic key is that patients with psychogenic responsiveness are behaviorly abnormal but physiologically normal. Not surprisingly, therefore, shouting, pinching and various other traumatic assaults have an unpredictable effect or none at all. This stands in contrast to the normal results of physical examination—normal breathing, intact pupils, preserved quick-phase nystagmus on caloric tests,[4] normal muscle resistance and stretch reflexes, and the absence of abnormal reflexes. Fisher[5] perceptively pointed out that such patients often actively close the eyelids when they are pressed open by the examining physician, whereas the lids shut more gently in true coma. If any doubt persists, it is reassuring to have a normal electroencephalogram and an examination of the cerebrospinal fluid. More invasive studies are unnecessary.

Does this clinical approach always work? Of course not—nothing in biology always works; but when it has not, we usually have found that the problem lay in our own not asking enough, not looking enough or not examining enough, rather than in our not plunging forward with more screening laboratory tests.

FRED PLUM, MD
Anne Parrish Titzell Professor of Neurology
New York Hospital-Cornell Medical Center

REFERENCES

1. Magoun HW: The Waking Brain, 2nd Ed. Springfield, Ill., Charles C Thomas, 1963
2. Mangold R, et al: Effects of sleep and lack of sleep on cerebral circulation and metabolism of normal young men. J Clin Invest 34:1092-1100, 1955
3. Plum F, Posner JB: The Diagnosis of Stupor and Coma, 2nd Ed. Philadelphia, Davis, 1972
4. Nelson JR: The minimal ice water caloric test. Neurology 19:577-585, 1969
5. Fisher CM: The neurological examination of the comatose patient. Acta Neurol Scand 45: Suppl 36:1-56, 1969

Idiopathic Polyneuritis

WITH THE DISAPPEARANCE of acute poliomyelitis in the United States since the institution of massive vaccination campaigns 15 years ago, idiopathic polyneuritis (Landry-Guillain-Barré syndrome) has become the most frequent cause of major paralytic disease. Idiopathic polyneuritis is doubly important to physicians because respiratory assistance and close medical attention are necessary for a time in a considerable proportion of patients, but full recovery without residual weakness may be anticipated in over 80 percent if the acute phase of the illness can be successfully bridged. In this issue of THE WESTERN JOURNAL OF MEDICINE, Rosenberg and Mendoza present a case in point in a Specialty Conference. The patient discussed was an adolescent boy with typical idiopathic polyneuritis who would surely have died without expert ventilatory assistance, but who at last report seemed well on the way to recovery. Although the ability to manage patients with idiopathic polyneuritis has improved considerably in recent years, our understanding of the

basic mechanism of the disorder is far from complete.

Interest in the pathogenesis of idiopathic polyneuritis has grown for half a century, with a veritable flood of studies appearing in the past five years, but the crucial questions have defied resolution. What are the nosologic limits of the entity? Is it one or several diseases? What is the common element in the apparent variety of precipitating events? What is the role of immunologic defense mechanisms? What other host factors are involved?

Several lines of evidence suggest that idiopathic polyneuritis, like experimental allergic neuritis, is mediated by sensitized lymphocytes, that is, is a disorder of delayed hypersensitivity. First, the pathological hallmark is perivenular lymphocytic and mononuclear cell infiltration.[1] Second, buffy coat cells from patients with idiopathic polyneuritis will regularly, but not always, demyelinate cultures of myelinating rat trigeminal ganglion.[2] Third, lymphocytes from patients with idiopathic polyneuritis will elaborate the lymphokinin, macrophage migration inhibitory factor, following exposure to sciatic nerve antigen (four of seven cases), but lymphocytes from patients with other neuropathies will not.[3] Similar kinds of evidence have been reported by Knowles and coworkers[4] and by Cook et al.[5] Fourth, recent electron microscopic studies have delineated how macrophages in the presence of lymphocytes destroy myelin sheath in a distinctive pattern which is identical both in idiopathic polyneuritis[6,7] and experimental allergic neuritis.[8]

Other lines of evidence either cast doubt on the delayed hypersensitivity concept or point to alternative, particularly humoral, mechanisms. Drachman et al[9] reported typical idiopathic polyneuritis occurring in a severely immunosuppressed patient who had undergone renal transplantation. Other well-documented examples have occurred in patients with Hodgkin's disease or lymphoma in whom serious immuno-deficiency would be expected. A host of other studies implicate circulating factors, presumably humoral antibodies, in idiopathic polyneuritis.[10-15]

Finally, preceding viral infection seems to play an important role in many cases. More than 50 percent of patients give a history of viral-like illness in the preceding one to four weeks. Usually such preceding illnesses remain undiagnosed, but many known viral infections have been followed by idiopathic polyneuritis including acute exanthems,[16] small pox vaccination,[17] Epstein-Barr virus infection,[18] cytomegalovirus,[19] and serum hepatitis.[20] Other non-viral preceding events have included surgical operation one to four weeks before,[21] antirabies vaccination containing dessicated rabbit spinal cord and roots,[22] fever therapy,[23] and mycoplasma infection.[24]

Tantalizing as these fragments of evidence are, they do not allow synthesis of a fully satisfying story. Nevertheless they suggest that some event, common to a wide range of trivial assaults upon the human body, triggers a misdirected immunological response that culminates in widespread peripheral myelin destruction.

ARTHUR K. ASBURY, MD
Professor and Vice-Chairman
Department of Neurology
University of California, San Francisco;
Chief, Neurology Service
San Francisco Veterans Administration Hospital

REFERENCES

1. Asbury AK, Arnason BG, Adams RD: The inflammatory lesion in idiopathic polyneuritis. Medicine 48:173-215, 1969

2. Arnason BGW, Winkler GF, Hadler NM: Cell-mediated demyelination of peripheral nerve in tissue culture. Lab Invest 21:1-10, 1969

3. Rocklin RE, Sheremata WA, Feldman RG, et al: The Guillain-Barré syndrome and multiple sclerosis: in vitro cellular responses to nervous-tissue antigens. N Engl J Med 284:803-808, 1971

4. Knowles M, Saunders M, Currie S, et al: Lymphocyte transformation in the Guillain-Barré syndrome. Lancet 2:1168-1170, 1969

5. Cook SD, Dowling PC, Whitaker JN: The Guillain-Barré syndrome: Relationship of circulating immunocytes to disease activity. Arch Neurol 22:470-474, 1970

6. Prineas JW: Acute idiopathic polyneuritis: An electron microscope study. Lab Invest 26:133-147, 1972

7. Wisniewski H, Terry RD, Whitaker JN, et al: Landry-Guillain-Barré syndrome: A primary demyelinating disease. Arch Neurol 21:269-276, 1969

8. Lampert PW: Mechanism of demyelination in experimental allergic neuritis: Electron microscopic studies. Lab Invest 20:127-138, 1969

9. Drachman DA, Paterson PY, Berlin BS, et al: Immunosuppression and the Guillain-Barré syndrome. Arch Neurol 23:385-393, 1970

10. Yonezawa T, Robbins N, Ishihara Y, et al: In vitro demyelination produced by sera from Landry-Guillain-Barré syndrome. Proc VIth Internat Congress Neuropathology 688-689, 1970

11. Tse KS, Arbesman CE, Tomasi TB, et al: Demonstration of antimyelin antibodies by immunofluorescence in Guillain-Barré syndrome. Clin Exp Immunol 8:881-887, 1971

12. Cook SD, Dowling PC, Murray MR, et al: Circulating demyelinating factors in acute idiopathic polyneuropathy. Arch Neurol 24:136-144, 1971

13. Dubois-Dalcq M, Buyse M. Buyse G, et al: The action of Guillain-Barré syndrome serum on myelin: A tissue culture and electron microscopic analysis. J Neurol Sci 13:67-83, 1971

14. Luijten JAFM, Baart De La Faille-Kuyper EH: The occurrence of IgM and complement factors along myelin sheaths of peripheral nerves: An immunohistochemical study of the Guillain-Barré syndrome. J Neurol Sci 15:219-224, 1972

15. Link H: Immunoglobulin abnormalities in the Guillain-Barré syndrome. J Neurol Sci 18:11-23, 1973

16. Miller HG, Stanton JB, Gibbons JL: Para-infectious encephalomyelitis and related syndromes. Quart J Med 25:427-504, 1956

17. Spillane JD, Wells CEC: The neurology of Jennerian vaccination. Brain 87:1-44, 1964

18. Grose C, Feorino PM: Epstein-Barr virus and Guillain-Barré syndrome. Lancet 2:1285-1287, 1972

19. Leonard JC, Tobin JO'H: Polyneuritis associated with cytomegalovirus infections. Quart J Med 40:435-442, 1971

20. Asbury AK: Hepatic neuropathy, Chapter *In* Peripheral

Neuropathy, P. J. Dyck, P. K. Thomas, and E. H. Lambert, Editors In press, 1973

21. Arnason BG, Asbury AK: Idiopathic polyneuritis after surgery. Arch Neurol 18:500-507, 1968

22. Appelbaum E, Greenberg M, Nelson J: Neurological complications following antirabies vaccination. JAMA 151:188-191, 1953

23. Garvey PH, Jones N, Warren SL: Polyradiculoneuritis (Guillain-Barré syndrome) following the use of sulfanilamide and fever therapy. JAMA 115:1955-1959, 1940

24. Steele JC, Gladstone RM, Thanasophon S, et al: Mycoplasma pneumoniae as a determinant of the Guillain-Barré syndrome. Lancet 2:710-713, 1969

PSRO—*Update 1974*

It is now a little more than a year since the Professional Standards Review Organization (PSRO) legislation went into effect. So far its implementation is on schedule. As required by PL 92-603, the PSRO areas were designated on 1 January 1974. The legislation gives practicing physicians priority in establishing the PSRO's for each of these areas at least until 1 January 1976. At that time the Secretary of the Department of Health, Education, and Welfare may designate other "qualified" public or non-profit organizations as the PSRO for a given area, as he deems it necessary.

The main interest of the Congress in adopting the PSRO legislation seems clear enough. It is to reduce the cost of the Medicare and Medicaid programs by imposing utilization controls on the services provided to the beneficiaries. The Senate Report on why the PSRO legislation was enacted states:

> "There is no question that the Government has a responsibility to establish mechanisms capable of assuring effective utilization review. Its responsibility is to millions of persons dependent upon Medicare or Medicaid, to the taxpayers who bear the burden of billions of dollars in annual program costs, and to the health care system."

The assumption that is made is also clear. It is assumed that simply by eliminating excessive utilization the cost of these programs will somehow be contained, and it is assumed that this can be done without impairment of quality. However, there are many physicians who seriously question the validity of these assumptions, and there is considerable reason to believe that quality and cost are closely and inextricably linked in medical care.

The PSRO legislation also addresses itself to the quality of the medical care for which payments are to be made under Medicare, Medicaid and Maternal and Child Health programs. This aspect is emphasized in a brochure recently given wide distribution to physicians by the Assistant Secretary for Health. The brochure states:

> "The primary emphasis of the PSRO program is on assuring the quality of medical care. Providing quality care may increase health services for some patients in certain areas and could increase costs in those circumstances.
>
> "A PSRO will be concerned also with whether medical care is necessary and delivered in the proper setting. If overuse or uneconomical use of services are identified and eliminated, cost savings will result.
>
> "A PSRO will not concern itself in any way with the fees for services charged by physicians or institutions."

Cost containment and quality assurance are both desirable and essential. But if it should happen to turn out that assuring quality and reducing costs cannot be accomplished at the same time by the means proposed by the PSRO legislation, many physicians believe that something of a crunch may be anticipated. In these circumstances it is quite possible that practicing physicians and the medical profession may be held responsible and to blame for the failure. This is hardly a comforting prospect for working doctors who are already the hapless victims of discriminating fiscal sanctions imposed by a more or less arbitrary government, and from which the medical profession is still finding itself with little or no recourse.

To accomplish its goals the approach of the PSRO legislation is to develop norms and standards for medical care. Initially these are to be established locally to meet local customs and needs as determined by the locally designated PSRO, but it is clearly expected that regional and perhaps even national standards will eventually ensue. The assumption seems to be that similar cases can be given similar care and that this will somehow be more economical, and that dissimilar cases requiring dissimilar case care will somehow be handled as occasional exceptions by the local PSRO. These assumptions of course strike at the heart of medical practice and medical care. A basic question is whether the good quality of care to which most Americans are accustomed and to which all Americans aspire can ever really be standardized, or if quality is to be preserved, will the exceptions

prove to be the rule. There are many physicians, in practice where the action is, who believe that good medical care cannot be standardized, but rather should always remain an individual matter to be worked out by a responsible physician with the informed consent of his patient.

The reaction of the medical profession to all this is quite predictable. We find ourselves in an unpleasant and very likely an impossible bind. On the one hand physicians have always insisted that only practicing physicians can decide what care should be given and whether what was given in a particular circumstance is appropriate. This is an oft stated position of the medical profession and the opportunity to fulfill this role within the PSRO legislation is not to be lightly put aside. But on the other hand there is an uncomfortable awareness that the assumptions underlying this legislation are quite likely not valid, and it is even more discomforting to know that the knowledge and technology needed to do this sort of thing at all is only crudely developed, let alone properly tested or perfected. And the threat of the PSRO legislation that, unless practicing physicians perform to the satisfaction of the federal government, the operation of local PSRO's will be taken out of our hands, produces an unprecedented dilemma for a proud, honored, respected, truth-seeking and successful profession. Caught in such a bind, it is little wonder that the official American Medical Association policy is to work for repeal or amendment of PL 92-603, and also and at the same time to try to make it work in order that physicians, not government bureaucrats, may remain the arbiters of quality in patient care.

It is much too early to predict the outcome. Repeal of the legislation seems unlikely. Amendment is more possible, although just what the amendments might be is by no means clear. In the meantime if PSRO's come into being, as it seems they will either under medical or other auspices, there is little doubt that whatever happens in PSRO's will significantly influence patient care and medical practice in whatever may be the future of our health care system. For this reason if for no other it would seem that there is now a real responsibility for practicing physicians, and for the medical profession as a whole, to do what they can to guide and shape the PSRO influence upon this future, regardless of the ultimate fate of PSRO's themselves. This is something that we as individual physicians and as a profession as a whole can do to serve not only our patients, but the people of this nation. It is a goal worthy of our profession in these difficult, frustrating and often exasperating times.

—MSMW

On Justice in Medical Care

In his essay "A New Ethic for Medicine?" published elsewhere in this issue, the Reverend Dr. Albert Jonsen introduces a new and important dimension into the current discussion of ethical problems in medical practice and medical care. In the role of a professional ethicist he has observed and studied a number of the emerging problems of morality in medicine first-hand, where the action is—in the hospital, in the operating room and in the intensive care unit. He reemphasizes the concept of justice (which he notes has been there all the time) and calls attention to the wide extent of the possible and appropriate applications of this ethical and moral principle throughout medical practice, medical care and what he identifies as the institution of medicine. There is much food for thought in Dr. Jonsen's essay and it is worth a careful reading by practicing physicians, the policy makers for the profession, and others who may be interested in finding fair and equitable solutions for some of the ethical dilemmas modern science and modern society are creating for modern medicine.

—MSMW

CASE REPORTS

Refer to: Abrams DE, Silcott RB, Terry R, et al: Antacid induction of phosphate depletion syndrome in renal failure. West J Med 120:157-160, Feb 1974

Antacid Induction of Phosphate Depletion Syndrome in Renal Failure

DAVID E. ABRAMS, MD
ROBERT B. SILCOTT, MD
R. TERRY, MD
THOMAS V. BERNE, MD
BENJAMIN H. BARBOUR, MD
Los Angeles

DESPITE THE TENDENCY toward phosphate retention in chronic renal insufficiency, it has been shown that a state of phosphate depletion with its concomitant clinical sequelae can be produced in uremic patients by the use of phosphate binding antacids.[1-3] Moreover, symptoms of the phosphorus depletion syndrome—weakness, bone pain, malaise and mental depression—appeared to be reversible by phosphate repletion.[2,3] Osteomalacia or rickets or both have been described in patients who have phosphorus deficiency from either a renal loss or gastrointestinal losses.[4,5] Bone changes, however, have not been documented from phosphate depletion in uremia.

The promotion of gastrointestinal loss of phosphorus by aluminum hydroxide has led to its use as an acceptable therapeutic agent in patients who have hyperphosphatemia; and, in fact, it is widely employed in uremic patients as a means of controlling hyperphosphatemia.[6] Osteomalacia and osteitis fibrosa are both commonly identified in histologic sections of bone from these patients.[7,8] It is believed that osteomalacia is more common when dietary calcium is low and that low serum calcium and phosphorus ion product predisposes the bone to its development.[9] In the present study, phosphorus depletion and osteomalacia with bone fractures developed in a patient on chronic hemodialysis who was receiving aluminum hydroxide therapy.

From the Departments of Internal Medicine, Pathology and Surgery, Los Angeles County-University of Southern California Medical Center, Los Angeles.

Submitted revised July 31, 1973.

Reprint requests to: B. H. Barbour, MD, Renal Section, Department of Medicine, USC School of Medicine, Los Angeles County-USC Medical Center, 1200 North State Street, Los Angeles, CA 90033

Report of a Case

The patient, a 42-year-old Mexican-American woman, was admitted to the Los Angeles County-University of Southern California Medical Center in June 1970 with complaint of fatigability and dyspnea. The illness which had progressed slowly during the preceding six months was characterized by increasing fatigue, weight loss, and loss of strength.

During the preceding four years the patient had had periodic attacks of arthritis involving the knees, wrists, ankles and great toe. She had taken colchicine with good relief, and had been told by her physician that she had gout. Except for periodic, temporary disability from her arthritic condition, she had been well until just before the onset of the present illness.

On examination at the time of admission the patient was observed to be short and mildly obese. She was sitting upright in bed, breathing rapidly and perspiring. Blood pressure was 108/90 mm of mercury, pulse 120, respirations 24, temperature 37°C (98.6°F). On funduscopic examination slight arteriolar narrowing was noted, but no hemorrhages or exudates. The neck veins were distended to the angle of the jaw with the patient in the sitting position, and the heart had a pronounced gallop rhythm. There were moist inspiratory rales heard on both sides of the chest. The liver was palpable 1 to 2 cm below the right costal margin. Moderate pretibial and ankle edema was noted. Gouty tophi were not seen. The knees and ankles showed some hypertrophy, though there was no limitation of motion.

Hemoglobin content was 8.8 grams per 100 ml

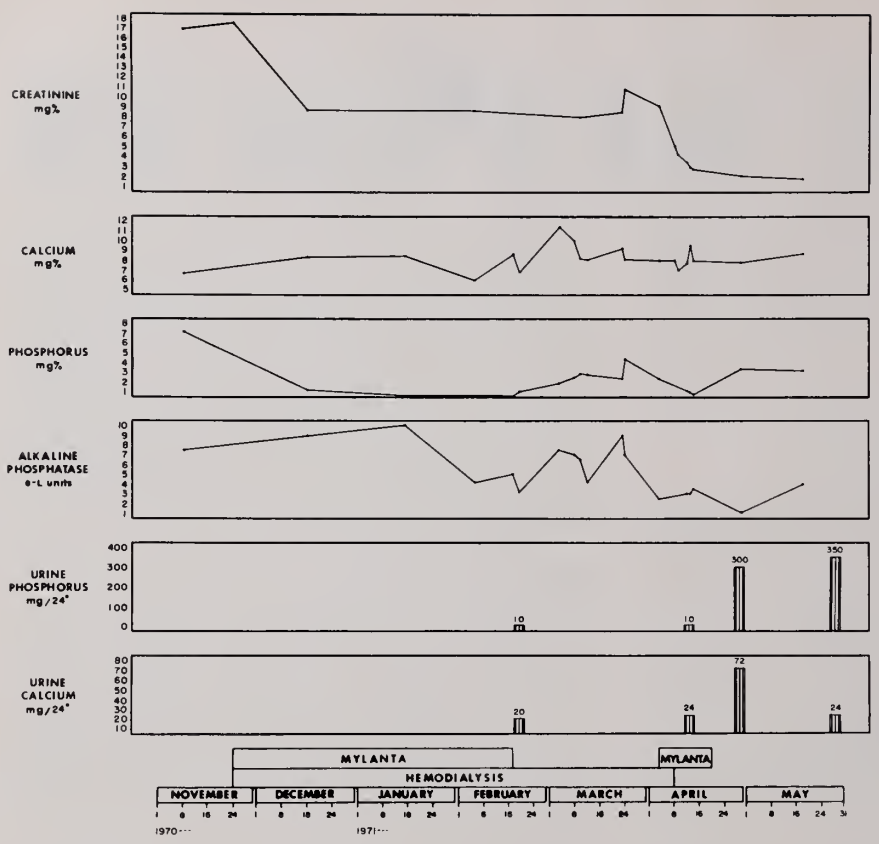


Chart 1.—Clinical course of patient with antacid-induced hypophosphatemia syndrome.

of blood, the hematocrit 27 percent, and leukocyte count, 7,800 per cu mm. The urine pH was 7.0, specific gravity 1.008 and the albumin reaction 2+. Microscopic examination of a centrifuged specimen showed 9 to 12 red blood cells and 1 to 2 leukocytes per high-power field, but no casts or crystals. No organisms grew on a culture of urine. The serum creatinine was 9.8 mg, uric acid 9.6 mg, serum albumin 3.2 grams, globulin 3.4 grams, alkaline phosphatase 3.5 Bessy-Lowry units, calcium 7.6 mg, phosphorus 5.5 mg and blood urea nitrogen 55 mg per 100 ml. Sodium content was 143 mEq, potassium 4.9 mEq and bicarbonate 21 mEq per liter.

An x-ray film showed slight cardiac enlargement and patchy infiltrates in both lower lung fields. Sinus rhythm with inverted T-waves in leads I, II, AVL and V 3-6 were shown on an electrocardiogram. An intravenous pyelogram showed the kidneys as small and contracted, each measuring 10 cm longitudinally. The calyceal system was not visualized.

The patient was treated with digoxin, furosemide, bed rest and a 40 mEq sodium diet. The clinical course is shown in Chart 1.

The patient was observed periodically over the succeeding five months while taking allopurinal, furosemide and ferrous sulfate. Hemodialysis was begun in November 1970 when serum creatinine was 16.9 mg per 100 ml; and, since serum phosphorus was 8.0 mg per 100 ml before dialysis was begun, Mylanta® was prescribed (each tablet contains magnesium hydroxide, 200 mg; aluminum hydroxide, 200 mg; and simethicone, 20 mg). The patient was treated for five hours, three times weekly, with a high performance parallel plate hemodialyzer.* After approximately six weeks of maintenance hemodialysis and Mylanta therapy, it was discovered that serum phosphorus had fallen to 2 mg per 100 ml (December 1970). Later the following month the patient began to complain of profound weakness and bone pain. She now walked with a waddling gait. Serum phosphorus was by then less than 0.5 mg per 100 ml and x-ray films of the pelvis showed a fracture of the inferior ramus of the ischium (Figure 1). Although this lesion had not been appreciated when the patient was initially evaluated in June 1970, in retrospect a pseudofracture in that location may well have been present. This finding

*D 4 Parallel Plate Dialyzer, manufactured by Life Med Division, American Hospital Supply.

Figure 1.—The top photograph was taken in July, 1970; the bottom photograph in January, 1971. A fracture of the left inferior ramus of the pubic bone is seen in the bottom photograph. A pseudofracture in the same location can be discerned in the earlier film.

together with the low calcium-phosphorus ion product was felt to be diagnostic of osteomalacia underlying the patient's condition at the time of the bone fracture.

On further questioning the patient said that she had taken Mylanta in amounts up to 75 tablets daily. She gave a history of having eaten clay, sand and adobe periodically since childhood. The Mylanta tablets gave the patient a certain satisfaction, reminiscent of the sensation she derived from pica. Mylanta was discontinued in mid-February 1971, and the serum phosphorus then rose toward the levels usually seen in patients on maintenance hemodialysis. In addition, the patient gained strength, increased her activity and no longer complained of bone pain. The following month the patient underwent cadaveric renal homotransplantation, and Mylanta was given again as a prophylactic agent against peptic ulceration, since corticosteroids were being given for immunosuppression. Despite careful instructions given to the patient for the use of Mylanta during this period, the urinary phosphorus fell to less than 50 mg daily and hypophosphatemia recurred (serum phosphorus 0.7 mg per 100 ml). A rib biopsy revealed severe osteomalacia. Figure 2 shows the changes demonstrable in a decalcified specimen by use of an azan stain compared with the changes seen with an ordinary hematoxylin and eosin stain.[10] Osteoid stains blue with the azan stain. (In the photograph here shown it is the light gray area around the Haversian canal.) After Mylanta was discontinued, the phosphorus level became normal.

Discussion

Phosphorus depletion induced by ingestion of antacid preparations has been reported in four cases without azotemia,[11-14] and in four cases with renal failure.[1-3] In two cases the patients were undergoing maintenance hemodialysis, but there was no mention of bone abnormalities. In the present case a fracture developed and there was biopsy evidence of osteomalacia. Furthermore, muscle weakness, anorexia and mental depression developed after phosphate depletion from antacids while the patient was undergoing maintenance hemodialysis. The recognition of this syndrome in patients on maintenance hemodialysis is especially important in view of the widespread use of nonabsorbable antacids among them. One of the previously mentioned reports[2] indicated that erythrocyte adenosine triphosphate (ATP) depletion may be induced by antacid-induced phosphate de-

pletion, and that the loss of intracellular ATP could be responsible for the clinical syndrome associated with phosphorus deficiency. Bone lesions were not reported in that case, however.

Osteodystrophy in patients receiving maintenance hemodialysis is a widely recognized disorder, and osteomalacia and osteitis fibrosa, occurring singly and together, have been reported in such patients.[8,15,16] Therefore, the occurrence of osteomalacia itself is not surprising,[11] but a spontaneously developing pelvic fracture is unusual. Pendras[6] reported a spontaneous hip fracture in one of his patients on maintenance hemodialysis, but there was no mention of serum phosphorus content or of histologic examination of bone, nor was there an indication that the patient was taking non-absorbable antacids. In the case reported herein, since the fracture was through what was probably a pre-existing pseudofracture, it is likely that the antacid-induced phosphate deficiency aggravated the osteomalacia and increased the hazard of fracture.

Monitoring the serum phosphorus at bimonthly or monthly intervals is important when a patient on maintenance hemodialysis is being treated with non-absorbable antacids.[17] Furthermore, as suggested by Alfrey,[18] aluminum phosphate might be substituted for other antacids postoperatively in transplant patients if the serum phosphorus falls below normal. The combination of corticosteroids, with their osteoporotic effect, and low serum phosphorus would predispose to fractures.

Summary

A patient receiving maintenance hemodialysis treatment was twice found to have serum phosphorus of less than 1.0 mg per 100 ml, associated with symptoms of bone pain, weakness and waddling gait. The patient was found to have been ingesting large quantities of an antacid preparation containing aluminum hydroxide. When that was discontinued, serum phosphorus returned to normal levels.

At the time of maximum depression of the serum phosphorus a spontaneous fracture of the ischium was detected. Twelfth rib biopsy was performed during the second episode of profound hypophosphatemia. Hematoxylin and eosin as well as azan stains of the rib sections demonstrated profound osteomalacia. Previous reports of the phosphorus depletion syndrome in experimental animals as well as man have mentioned osteomalacia as a concomitant feature. In renal failure where osteomalacia is already a frequent complication, care must be taken not to aggravate this tendency by permitting phosphorus depletion through the use of these antacid preparations.

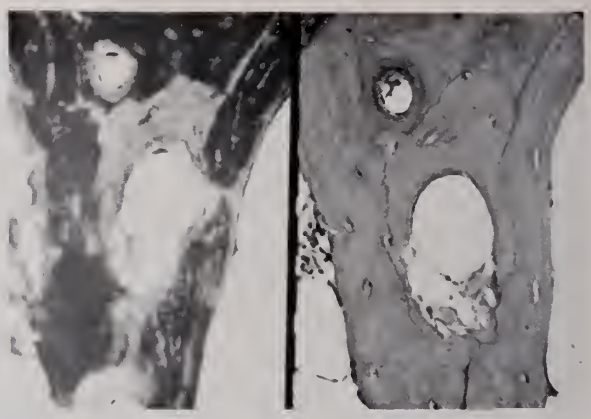


Figure 2.—These bone sections were taken from adjacent slices and stained with azan (left side) and hematoxylin and eosin (right side) respectively. Osteomalacia is identified in the azan stained specimen by the lightly stained area extending eccentrically around the central canal and along the bone margins. This is less clearly seen in the H & E stained specimen.

REFERENCES

1. Dodge WF, Travis L: Iatrogenic hypophosphatemia in infants with renal insufficiency. Ped 35:792-794, May 1965

2. Lichtman MA, Miller DR, Freeman RB: Erythrocyte adenosine triphosphate depletion during hypophosphatemia in a uremic subject. N Engl J Med 280:240-244, Jan 1969

3. Boelens PA, Norwood WK, Kjellstrand C, et al: Hypophosphatemia with muscle weakness due to antacids and hemodialysis. Am J Dis Child 120:350-353, Oct 1970

4. Dent CE: Rickets and osteomalacia from renal tubule defects. J Bone & Joint Surg 34B:266-274, May 1952

5. Lotz M, Zisman E, Bartter FC: Evidence for a phosphorus-depletion syndrome in man. N Engl J Med 278:409-415, Feb 1968

6. Pendras JP, Erickson RV: Hemodialysis: A successful therapy for chronic uremia. Ann Int Med 64:293-311, Feb 1966

7. Follis RH Jr, Jackson DA: Renal osteomalacia and osteitis fibrosa in adults. Bull Johns Hopkins Hosp 72:232-241, Apr 1943

8. Duursma SA, Visser WJ, Njio L: A quantitative histologic study of bone in 30 patients with renal insufficiency. Calc Tiss Res 9:216-225, 1972

9. Standbury SW, Lund GA: Parathyroid function in chronic renal failure. Quart J Med 35:1-23, Jan 1966

10. Bartelheimer H, Schmitt-Rohde JM: Die Biopsie des Knochens als differential diagnostische klinische Methode. Klinische Wochenschrift 35:429-440, May 1957

11. Bloom WL, Flinchum D: Osteomalacia with pseudofractures caused by the ingestion of aluminum hydroxide. JAMA 174:1327-1330, Nov 1960

12. Lotz M, Ney R, Bartter FC: Osteomalacia and debility resulting from phosphorus depletion. Trans A Am Physicians 77: 281-295, 1964

13. Ludwig GD, Kyle GC, de Blanco M: "Tertiary" hyperparathyroidism induced by osteomalacia resulting from phosphorus depletion. AM J Med 43:136-140, Jan 1967

14. Ansari A: Antacid-induced phosphorus depletion and repletion. Minn Med 53:837-838, Aug 1970

15. Jowsey J, Massrey SG, Coburn JW, et al: Microradiographic studies of bone in renal osteo dystrophy. Arch Intern Med 124: 539-543, Nov 1969

16. DeVeber GA, Oreopoulos DG, Rabinovich S, et al: Changing patterns of renal osteodystrophy with chronic hemodialysis. Trans Am Soc Artif Intern Organ 15:479-485, 1970

17. Goldsmith RS, Furszyfer J, Johnson WJ, et al: Control of secondary hyperparathyroidism during long term hemodialysis. Am J Med 50:692-699, May 1971

18. Alfrey AC, Jenkins D, Groth CG, et al: Resolution of hyperparathyroidism renal osteodystrophy and metastatic calcification after renal homotransplantation. N Engl J Med 279:1349-1356, Dec 1968

Refer to: Dreyfus PM, Senter TP: Acute cerebellar ataxia of childhood—An unusual case of varicella. West J Med 120:161-163, Feb 1974

Acute Cerebellar Ataxia of Childhood

An Unusual Case of Varicella

PIERRE M. DREYFUS, MD
THOMAS P. SENTER, MD
Davis, California

CEREBELLAR ATAXIA of acute onset (acute cerebellitis) is a relatively common neurological disorder among children.[1] A viral cause has been postulated even though the infectious agent has been identified or isolated in only a minority of cases. Several different viruses have been incriminated: varicella (chicken pox), ECHO type 9, coxsackie B, poliomyelitis, measles, mumps and rubella.[1] Of these, varicella appears to be the one most commonly identified. Cerebellar symptoms have been noted in 25 to 30 percent of cases of varicella encephalitis.[2,3] While the exanthematous manifestations of the disease usually precede the advent of neurological symptoms and signs,[4,5] on very rare occasions the sequence of events is reversed.[6] It is the purpose of this brief communication to describe a case of acute cerebellar ataxia in which the skin lesions of varicella did not appear until ten days after the onset of ataxia, lethargy and vomiting.

Report of a Case

The patient was a 6-year-old boy brought to the Sacramento Medical Center because of difficulty in walking, slurred speech and lethargy which had gradually increased over a two-day period.

The patient had been in excellent health until two days before admission, when he had an episode of vomiting early in the morning and then fell asleep on the living room floor. He was roused and went to school, where he had another episode of vomiting. When he came home in the afternoon he was put to bed and slept through the night. The next day he was unable to walk and his speech was slurred and slow. He had two further episodes of vomiting that day, was lethargic and complained of dizziness and generalized head and neck pain. The following day the patient had several bouts of vomiting and his gait was noted to be extremely ataxic. This prompted admission to hospital.

During the admission examination the patient tended to fall asleep when left alone. However, he was found to be properly oriented and cooperative when stimulated. Blood pressure was 110/70 mm of mercury, pulse rate 100 per minute, respirations 20 per minute and temperature 37°C (98.6°F). The neck was supple. General physical examination failed to reveal any abnormality.

Neurological examination showed no abnormality of cranial nerves except for nystagmus on lateral gaze to either side. Fundi were normal. The patient could neither stand nor sit down when not assisted; he tended to fall backward or to either side. The gait was almost impossible to test because of pronounced unsteadiness: The patient stood on a broadened base and he swayed back and forth. Speech was slurred and difficult to understand. Finger to nose and heel to shin tests, as well as rapid alternating movements, betrayed severe cerebellar dysfunction bilaterally. There seemed to be a decrease in tone in all four extremities. Deep tendon reflexes were pendular in quality but symmetrical in both upper and lower extremities. Results of sensory examination were within normal limits. No pathological reflexes could be elicited.

The past medical history was essentially unremarkable, but a family history revealed that typical chicken pox skin lesions had developed in the patient's three siblings while he was in the hospital. One of the patient's brothers had been exposed to the virus at school before the onset of the patient's illness.

Laboratory data on admission revealed a normal blood cell count including leukocyte differential. Urinalysis was normal. Total serum protein, calcium, phosphorus, cholesterol uric acid, creatine, total bilirubin, creatine phosphokinase, SGOT, electrolytes, blood urea nitrogen, urine and blood for gas chromatography were all within normal limits. Alkaline phosphatase and lactic dehydrogenase activity were slightly elevated. A brain scan showed no abnormality. An electroencepha-

From the Departments of Neurology and Pediatrics, University of California, Davis, School of Medicine; and the Sacramento Medical Center.

Submitted April 17, 1973.

Reprint requests to: P. M. Dreyfus, MD, Department of Neurology, University of California, Davis, School of Medicine, Davis, CA 95616.

logram and x-ray films of the chest and skull were within normal limits.

A lumbar puncture performed on admission revealed clear, colorless spinal fluid under normal pressure containing 32 white cells per cu mm, of which 85 percent were lymphocytes and 15 percent polymorphonuclear leukocytes. The protein content was 22 mg per 100 ml and the sugar content 77 mg with a concomitant blood sugar of 106 mg per 100 ml. India ink preparation, cultures and cytology of cerebrospinal fluid were negative. No virus could be isolated from the spinal fluid. Another cerebrospinal fluid examination five days after admission revealed 9 white blood cells per cu mm, of which 7 were lymphocytes and 2 polymorphonuclear leukocytes.

Because of the history of exposure to chicken pox, the patient was scrutinized for the appearance of a vesicular eruption. During the first week, no lesions could be discerned and he continued to be decidedly ataxic and somewhat lethargic. Finally, eight days after admission to hospital, six small umbillicated vesicles broke out on the patient's arms, legs and trunk. A specimen of serum, drawn on admission, showed a varicella titer of 1:128 while titers to mumps and herpes simplex were not elevated.

The patient began to improve neurologically as soon as the varicella skin lesions appeared. Vomiting stopped, he gradually became less lethargic and his ataxia diminished. Varicella titer in a specimen of serum obtained on the day of discharge was 1:256. According to his parents, the patient began to walk more normally within two weeks following discharge from the hospital and was fully recovered after three months. In a six-month neurological follow-up no abnormal neurological symptoms or signs were noted except for some hyperactive behavior and an occasional temper tantrum.

Discussion

Neurological complications of varicella are relatively uncommon. Symptoms usually develop between three days and two weeks following the appearance of the skin rash.[4] Neurological symptoms precede the skin eruption only in very rare instances.[6] Central nervous system manifestations of varicella infection reflect involvement of the cerebrum, the cerebellum and the spinal cord (encephalomyelitis). Cerebral symptoms most commonly include irritability, stupor, delirium, hemiparesis, generalized seizures and choreo-athetoid movements. In some instances of varicella encephalopathy coma, decerebrate rigidity and death may ensue. Paraplegia, spasticity and sensory signs constitute the most common spinal manifestations. The latter may occur separately or in association with cerebral symptoms. Pure cerebellar symptoms consisting of tremulousness and generalized ataxia seem to occur more frequently than do symptoms referable to either the cerebrum or the spinal cord. The cerebellar syndrome associated with varicella tends to be benign and self-limiting. The patient usually recovers completely.

It is generally recognized that the neurological complications of varicella include several distinct clinical entities. Those which either precede or accompany the exanthematous manifestations of the disease, described above, seem to be directly related to viral invasion of the nervous system, while others which usually occur after the cutaneous lesions are either well established or vanishing, are most likely caused by a non-specific post-infectious, auto-immune disease process. The latter may involve the optic nerves (retrobulbar neuritis), the cerebrum and brain stem, the spinal cord (acute transverse myelitis) or the peripheral nervous system (post-infectious polyneuritis of the Guillain-Barré type).

The neuropathological attributes of varicella encephalomyelitis suggest direct invasion of the nervous system,[7] although a post-infectious process of auto-immune type characterized by a perivascular inflammatory response and demyelination appears to be present in most cases of varicella encephalomyelitis in which pathologic examination is done.[8] In the case under discussion, it seems reasonable to assume that the patient's acute cerebellar syndrome was caused by direct invasion of the Varicella-Zoster virus which, by hematogenous dissemination, affected the central nervous system before the skin. In view of the sequence of events, a post-infectious, anto-immune process seems less likely. It is noteworthy that to date no electron microscopic or fluorescent antibody studies of postmortem neural tissue obtained from a case of varicella encephalomyelitis have been reported and that it has not been possible to isolate the varicella virus from such tissue or from cerebrospinal fluid of patients afflicted with the disease.[8]

The onset of neurologic complications before the appearance of the typical skin rash of varicella has been reported previously.[6] However, the

pathogenesis of pre-eruptive neurological complications of varicella continues to be essentially unknown.

REFERENCES

1. Bell WE: Ataxia in childhood—Clinical approach and differential diagnosis. Lancet 85:2, 1965
2. Appelbaum E, Rachelson MH, Dolgopol VB: Varicella encephalitis. Am J Med 15:223, 1953
3. Underwood E: The neurological complications of varicella. Br J Dis Childh 32:83,177,241, 1935
4. Gibble H, Kramer B, Naji AF: Encephalitis complicating chicken pox—Report of a case with death two and a half years later and review of the literature. Am J Dis Childh 99:137, 1960
5. Heppelston, JD, Pearce KM, Yates PO: Varicella encephalitis. Arch Dis Childh 34:318, 1959
6. Goldston, AS, Millichap JG, Miller RH: Cerebellar ataxia with pre-eruptive varicella. Am J Dis Childh 106:197, 1963
7. McCormick WF, Rodnitzky RL, Schochet SS Jr, et al: Varicella Zoster encephalomyelitis—A morphologic and virologic study. Arch Neurol 21:559, 1969
8. Griffith JF, Salam M, Adams RD: The neurology of varicella. Acta Neurol Scand 46:279, 1970

Refer to: Bick RL, Adams T: Histiocytic medullary reticulosis in two Chinese women. West J Med 120:163-166, Feb 1974

Histiocytic Medullary Reticulosis in Two Chinese Women

RODGER L. BICK, MD, *Bakersfield, California*
THOMPSON ADAMS, MD, *Los Angeles*

HISTIOCYTIC MEDULLARY RETICULOSIS (HMR) is a rare hematological malignant disease. Only 60 cases have been reported. Scott and Robb-Smith were the first to recognize HMR as a distinct entity when they reported six cases in 1939.[1] Since then various observers have reported sporadic cases and these combined reports have given rise to a concept of the clinical and morphological features of HMR. There are no pathognomonic findings; diagnosis comes from suggestive clinical features coupled with morphologic characteristics.

Clinically, HMR may be insidious in onset, with fatigue and weight loss the only early symptoms, but often the patients present with hectic fevers and night sweats. Fever at some time in the early course of the disease is a characteristic feature and tends to be moderate to severe and either intermittent or unrelenting. Common physical findings in HMR are moderate to pronounced and progressive splenomegaly, reported in more than 90 percent of patients, hepatomegaly in 75 percent, and a surprising absence of widespread lymphadenopathy in most cases.[2-4]

The hematological findings of HMR follow a characteristic pattern with the vast majority of patients presenting with pancytopenia of the peripheral blood. The anemia, normochromic and normocytic, is commonly associated with a hemoglobin of less than 10 grams per 100 ml. The thrombocytopenia is usually moderate and although bleeding is not typical in HMR, it can occur. The neutropenia is in the range of 2,000 to 2,500 cells per cu mm and the differential is usually normal. Bone marrow examination typically reveals a diffuse increase of histiocytes, these cells often making up from 10 to 80 percent of the marrow elements. As many as 10 to 20 percent of the histiocytes will be engaged in phagocytosis, primarily of erythroid elements, but phagocytosis of platelets and myeloid elements is also common. The demonstration of phagocytosis represents the characteristic morphologic feature of HMR and this must be observed before a diagnosis is made. Additional marrow findings usually include erythroid hyperplasia and abundant megakaryocytes.

Biopsy of the liver and autopsy specimens of liver, spleen, and often other reticuloendothelial tissue likewise reveals an increase in histiocytes engaged in phagocytosis of erythroid, myeloid, and platelet elements. Phagocytosis of these elements by histiocytes is thought, by most observers, to account for the anemia, neutropenia, and thrombocytopenia of HMR.[5,6] Although several reports have mentioned the finding of occasional histiocytic cells in the peripheral blood, a leukemic phase of this disease has not been reported.

Clinically, HMR is a rapidly fatal disease which remains unresponsive to therapy and death usually occurs within a year of the diagnosis. Numerous cytotoxic agents have been tried in this disorder, but remissions, if induced at all, have been very brief and no chemotherapeutic regimen has been uniformly successful in improving survival. Radiation therapy is not commented upon in many reports, and when it was employed the benefit was not clear.

The largest single series of HMR comes from China and assembles the entire Chinese experience

From the Division of Hematology, Department of Medicine, University of California, Los Angeles, Center for the Health Sciences.

Supported by USPHS Grant Number AM-05112.

Submitted May 30, 1973.

Reprint requests to: R. L. Bick, MD, Kern County General Hospital, 1830 E. Flower St., Bakersfield, CA 93305.

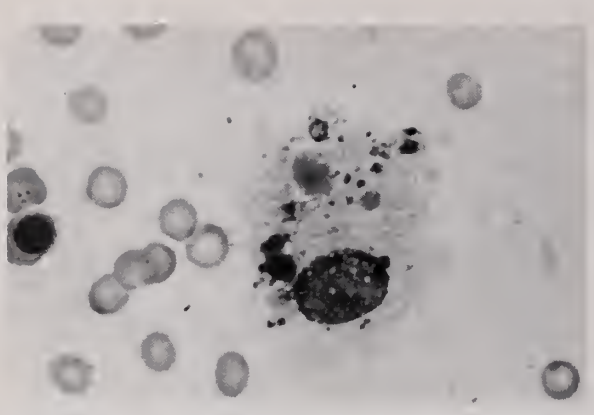


Figure 1.—Marrow histiocyte (Case 1) showing phagocytosis of erythrocytes, platelets, and probably two neutrophils.

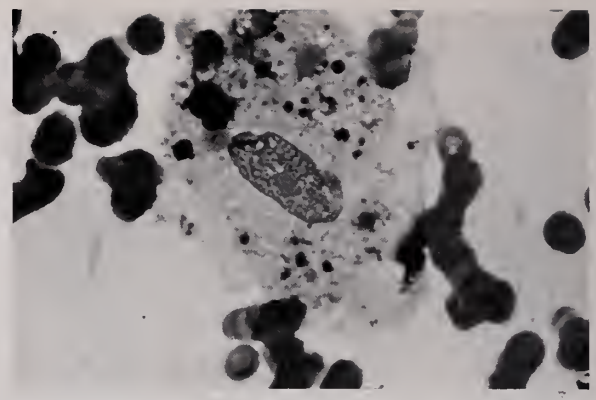


Figure 2.—Marrow histiocyte (Case 1) showing phagocytosis of erythrocyte, myelocyte, and numerous platelets.

with this disorder; in this series of 18 cases there was only one female patient.[4]

The two cases here reported were in Chinese-born women with the characteristic clinical and morphological features of HMR.

Reports of Cases

CASE 1. A 50-year-old Chinese woman consulted a private physician, two years before final admission, with complaint of a mass in the right side of the neck. Biopsy showed a node was supplanted by abnormal cells which were thought to represent lymphoblastic lymphoma. At that time a blood cell count was within normal limits with leukocytes 5,200 per cu mm, hemoglobin 12 grams per 100 ml, the hematocrit 37 percent, and the platelet count 125,000 per cu mm. A bone marrow examination was interpreted as normal. The patient was treated with irradiation, 2,500 R to the right side of the neck. She remained well for 24 months and then suddenly became ill with chills, night sweats, and fever of 40°C (104°F). At that time she was found to have significant hepatosplenomegaly and abdominal distension. Hemoglobin content was 8 grams per 100 ml of blood, the hematocrit 23 percent, leukocyte count of 4,400 per cu mm, and platelets 120,000 per cu mm. A bone marrow specimen was interpreted as normal by a pathologist. Suspecting relapse of lymphoma, the attending physician prescribed COP [cyclophosphamide + vincristine sulfate (Oncovin®) + prednisone] cyclic chemotherapy every three weeks as described by Luce and associates.[7] The course of illness remained unchanged for the following month except for progressive pancytopenia (hemoglobin 6 grams per 100 ml, leukocytes 4,000 per cu mm, and platelets 65,000 per cu mm). Over the next six weeks the patient received two more courses of chemotherapy without resolution of fever, anemia or thrombocytopenia; and at that time she was found to have progressing hepatosplenomegaly but no lymphadenopathy. Platelets decreased to 21,000 per cu mm and transfusions were necessary to keep the hemoglobin content above 10 grams per 100 ml. She was then transferred to UCLA where the same findings were noted. She remained acutely ill, with fever to 40°C.

Numerous cultures were obtained including studies for cytomegalovirus, histoplasmosis, toxoplasmosis, and pneumocystis carinii. All such studies were negative and the fever remained unexplained. Administration of bleomycin sulphate (NSC 125066) was begun at a dose of 15 mg per square meter twice a week. At this time leukocytes numbered 1,500 per cu mm, hemoglobin was 9.6 grams per 100 ml, the hematocrit was 28 percent, and the platelet count 10,000 per cu mm. Liver function tests were abnormal, with pronounced elevation of the serum glutamic oxalic transaminase, lactic dehydrogenase and alkaline phosphatase. A bone marrow examination revealed a large number of histiocytes, accounting for approximately 20 percent of nucleated cells. Many of these histiocytes were engaged in phagocytosis of erythroid, myeloid, and thrombocyte elements. Representative examples of this phagocytosis are shown in Figures 1 and 2.

After three weeks of therapy (six doses of bleomycin) the patient had not improved and hepatosplenomegaly progressed without the development of lymphadenopathy. By the end of the third week of therapy the leukocyte count had decreased to 525 and the platelet count to 5,000

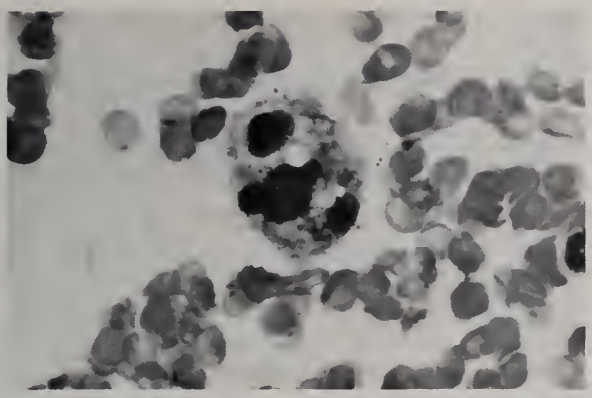


Figure 3.—Marrow histiocyte (Case 2) showing phagocytosis of two nucleated red cells and a segmented neutrophil.

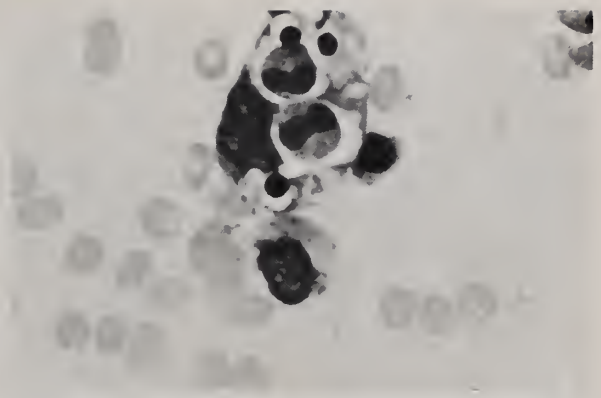


Figure 4.—Marrow histiocyte (Case 2) showing phagocytosis of two neutrophils and three nucleated erythrocytes.

per cu mm; and in spite of transfusions the hemoglobin was 8.9 grams per 100 ml. She died of respiratory failure at this time.

CASE 2. The patient, a 24-year-old Chinese woman, had been admitted to UCLA seven months before the final admission. On the initial she had had fever, chills, and profuse night sweats for three weeks and had had a lump in neck for one week. Her past history was negative except for a positive tuberculin skin test one year earlier, because of which she was receiving isoniazid. On physical examination at that time left cervical and right inguinal adenopathy were noted. Leukocytes numbered 2,700 and platelets 130,000 per cu mm, and the hemoglobin content was 10 grams per 100 ml. Results of liver function tests were abnormal, with elevation of the SGOT, SGPT, and alkaline phosphatase. Bilirubin, serum proteins and serum protein electrophoretic pattern were within normal limits. A liver-spleen scan showed moderate hepatomegaly but not splenomegaly. An x-ray film of the chest was normal and an intravenous pyelogram showed slight deviation of the right ureter. Numerous cultures were obtained and an investigation for infection included studies for cytomegalovirus, histoplasmosis, toxoplasmosis, and cultures for tuberculosis and fungi. None of these studies were positive and the fever remained unexplained.

Biopsy of the liver and of a left cervical lymph node showed diffuse histiocytosis, with erythrophagocytosis being noted in the liver specimens. Bone marrow examination was initially interpreted as showing only reactive myeloid elements. Because of the pathologic changes in the lymph node, and particularly the liver, the patient was diagnosed as having histiocytic lymphoma, suggestive of HMR, and was treated with cyclophosphamide 100 mg a day and prednisone 40 mg a day by mouth. She showed some symptomatic improvement but the lymphadenopathy progressed. Two months later the prednisone and cyclophosphamide were discontinued and irradiation was administered—4,500 R to the left cervical and right inguinal areas. During the following month adenopathy continued to progress and COP therapy as described in Case 1 was begun. There was then temporary resolution of adenopathy, but four weeks later it reappeared despite continued combination chemotherapy. At this time an abdominal mass developed and it progressed to obstruction of the small bowel. The patient then received 800 R to the abdomen with improvement in symptoms, and she was given BCNU (NSC-409962, bischlorethyl-nitrosourea) 150 mg on day one followed by 75 mg on day three. She had no objective response and died of pancytopenia and bleeding seven months after initial presentation. At autopsy, histiocytic involvement of cervical, axillary, mesenteric, and aortic lymph nodes was noted, as well as histiocytosis in the jejunum, epicardium, liver, right renal pelvis, right adrenal gland, left ovary and inferior vena cava. On careful reappraisal of the initial bone marrow material, diffuse histiocytosis was noted, with histiocytes accounting for approximately 15 percent of nucleated elements. Many of these histiocytes were engaged in phagocytosis of erythroid, myeloid, and platelet forms. Figures 3 and 4 demonstrate representative marrow findings.

Discussion

These two cases demonstrate the rather typical clinical course and characteristic marrow findings

of HMR. Both patients had a progressively downhill course which was little changed by chemotherapeutics. Neither showed significant response to COP combination chemotherapy; one received bleomycin and the other received BCNU, both without demonstrable benefit. Unrelenting febrile episodes were unassociated with a detectable infectious agent and neither patient had improvement of the febrile course with either antibiotic or cytotoxic therapy. One patient had adenopathy but neither had adenopathy of the degree expected with widespread lymphomatous disease. Both patients had pancytopenia which progressed to a striking degree regardless of therapy.

In both of these patients the bone marrow was initially thought to be normal by experienced pathologists; however, careful retrospective examination of initial marrow specimens from both patients revealed the characteristic changes of HMR. It is noteworthy that in the specimens of marrow from both patients the increase in histiocytes was usually noted in areas surrounding marrow particles and in peripheral areas of the marrow smear. Very few histiocytic cells were actually found in the cellular centers and, in general, the histiocytosis and phagocytosis, although quite striking, were obviously patchy. For this reason it is suggested that in all cases of suspected histiocytic lymphomas the marrow be examined painstakingly to detect phagocytosis of cellular elements which might not be apparent during routine examination of the most cellular marrow particles.

The cause of HMR is unknown but most investigators consider it a malignant disease; some suggest that it is an atypical variant of histiocytic lymphoma. The prognosis is poorer and the survival shorter than for histiocytic lymphoma, however, and a further point of difference is that phagocytosis of platelets, erythroid and myeloid elements is not a characteristic finding in histiocytic lymphoma.[8]

HMR bears an unclear relationship to leukemic reticuloendotheliosis (histiocytic leukemia) but the two might be related in the same manner as are well differentiated lymphocytic lymphoma and chronic lymphocytic leukemia. If HMR and leukemic reticuloendotheliosis are related, however, it is clear that the leukemic form has a much better prognosis than the medullary disorder. The marrow of leukemic reticuloendotheliosis is easily differentiated from that of HMR in that not only is phagocytosis not seen,[9] several investigators have clearly demonstrated the cells of leukemic reticuloendotheliosis to be incapable of phagocytosis.[10,11] Furthermore, the marrow of reticuloendotheliosis tends to be hypocellular, difficult to aspirate, and often fibrotic, whereas in HMR the marrow is usually hypercellular. Clear clinical differences also exist, with more than 60 percent of patients with leukemic reticuloendotheliosis pursuing a subacute or chronic course and survivals of ten years not uncommon.[12] Although both diseases are associated with hepatosplenomegaly, leukemic reticuloendotheliosis is characterized by widespread lymphadenopathy while HMR is not.

HMR is thought to represent a rare subgroup of histiocytic lymphoma but it may actually be found to be more common than has been suspected when bone marrow specimens are more carefully searched for the typical morphological features of this disorder. It seems important to identify this disease correctly since there are obvious prognostic and possibly different therapeutic implications. Our patients as well as those described in the literature were resistant to the usual chemotherapeutic agents used in the treatment of lymphomas. Both of our patients had beneficial effects from radiation therapy. Procarbazine (Matulane®), which we did not use, has been reported to have antihistiocytic activity.[13]

REFERENCES

1. Scott RB, Robb-Smith AHF: Histocytic medullary reticulosis. Lancet 2:194-198, 1939
2. Scamps RA, O'Neill BJ, Purser BN: Histiocytic medullary reticulosis. Med J Australia 2:956-960, 1971
3. Asher R: Histiocytic medullary reticulosis: A case without lymphadenopathy. Lancet 1:650-651, 1946
4. Chih-Fei Y, Chung-Hung T, Hua-Teh H, Teh-Ts'ung T, Hsi-Lien K, Ch'iu-T'ang Y, Chieh L: Histiocytic medullary reticulosis. Chinese Med J 80:466-474, 1960
5. Natelson EA, Lynch EC, Hettig RA, et al: Histiocytic medullary reticulosis: The role of phagocytosis in pancytopenia. Arch Int Med 122:223-229, 1968
6. Lynch EC, Alfrey CP: Histiocytic medullary reticulosis—Hemolytic anemia due to erythrophagocytosis by histiocytes. Ann Int Med 63:666-671, 1965
7. Luce JK, Gamble JF, Wilson HE, et al: Combined cyclophosphamide, vincristine, and prednisone therapy of malignant lymphoma. Cancer 28:306-317, 1971
8. Rundles RW: Reticulum cell sarcoma, *In* Williams WJ (Ed): Hematology. pp 938-944, McGraw-Hill Book Co., N.Y., 1972
9. Vaithianathan T, Bolonik SJ, Gruhn JG: Leukemic reticuloendotheliosis. Am J Clin Path 38:605-611, 1962
10. Yam LT, Castoldi GL, Garvey MB, et al: Functional cytogenetic and cytochemical study of the leukemic reticulum cells. Blood 32:90-101, 1968
11. Yam LT, Li CY: Leukemic reticuloendotheliosis—The role of tartrate-resistant acid phosphatase in diagnosis and splenectomy in treatment. Arch Int Med 130:248-256, 1972
12. Bouroncle BA, Wiseman BK, Doan CA: Leukemic reticuloendotheliosis. Blood 13:609-670, 1958
13. Stolinski DC, Solomon J, Pugh RP, et al: Clinical experience with procarbazine in Hodgkin's disease, reticulum cell sarcoma and lymphosarcoma. Cancer 26:984-990, 1970

LETTERS *to the Editor*

Concerning Professional Competence

To the Editor: A letter from Dr. Felch (Calif Med 119:62, Nov 1973) deplores the use of involvement in continuing education experiences as a guide to the evaluation of physician competence —particularly as grounds for relicensure. He prefers the use of medical audit and patient care appraisal techniques as a form of examination. I would like to suggest that involvement in continuing education and appropriate testing procedures are complementary activities; one does not exclude the other but requires the other. In our present state of imperfection regarding techniques of examination, as well as techniques of education, it seems presumptuous to state that we now have even a fair answer in either area.

State society continuing education standards are motivating factors for participation in learning activities. It is quite possible that the chief value of any examination or "care appraisal program" is not its ability to "give the public the honest assurance of continued competence it demands," but rather to act also as a motivating factor to encourage physician involvement in continuing education. It is in this area that requirements for participation in continuing education, examinations, medical audit programs, etc. come together and should be recognized for what they are—simply an encouragement for further learning. One can distort requirements for continuing education and denigrate their true role. Similarly, one can distort and disrupt examination-appraisal processes as being unrealistic, unrelated to patient outcomes, cost-generating, etc., etc.

The sentiments expressed by Dr. Felch seem to be based on a feeling that a quantitation of continuing education effort will inhibit appropriate qualitative changes in this educational experience. It is hard to find any evidence for this. The ferment in the educational centers regarding methodology seems as bubbly as ever.

There is excitement and intense personal satisfaction from the maintenance of professional competence and there is a role for state and national specialty societies and for organized medicine to play. Involvement in continuing education is as close to being the one certainty for the next several decades as anything that can be told to a young physician today. On the other hand, it is quite possible that today's criteria for "good care" could be tomorrow's anachronisms.

Donald W. Petit, MD
Pasadena

* * *

The Author Replies

If Dr. Petit's point is that continuing medical education (CME) is important, there is no argument here. Obviously, it is essential for doctors to keep up with biomedical advances if they are to render high quality care.

The trouble is that most of CME is still teacher-oriented and academic. It may focus on what is new, but not necessarily on what is useful. There is much unhappy evidence that the recipient (even if he is present, awake and receptive) retains little and is unlikely to change his behavior when he returns to the real world of practice.

It follows that a system which provides "motivating factors for participation" in such CME programs may end up giving credit for something that may be meaningless. And this is why the American Society of Internal Medicine is leary of using such a system for qualification for state society [medical association] membership and, particularly, for relicensure.

In tomorrow's world, actual physician performance (and its impact on patient outcomes) will be measured, specific deficits uncovered, specific remedial CME applied, and CME's impact on behavior change in turn measured. Only then will we be able to be totally honest in our assertions of accountability to the public.

William C. Felch, MD
President, American Society of Internal Medicine

Hypoglycemia in Renal Disease

To the Editor: Dr. Swerdloff has outlined rather comprehensively the mechanism of hypoglycemia in diabetic patients in the review, "The Obese Diabetic" (Bray GA, et al: Calif Med 119:14-47, Oct 1973). He points out that tolbutamide, acetahexamide, chlorpropamide and tolazamide may produce hypoglycemia in patients with renal dis-

ease. The subject of hypoglycemia in renal disease is an interesting one. To cite some examples:

- White and Kurtzman[1] reported the case of a non-diabetic azotemic patient who developed symptomatic hypoglycemia on hemodialysis.
- Gutman et al[2] and Rigg and Bercu[3] described hypoglycemia after hemodialysis with high dialysis bath glucose concentrations.
- David et al[4] have reported aspirin induced hypoglycemia in a patient on hemodialysis.
- Block and Rubenstein[5] have noted spontaneous hypoglycemia in diabetic patients with renal insufficiency.
- Greenblatt[6] reported fatal hypoglycemia occurring in a patient after peritoneal dialysis.

Although the exact mechanism of hypoglycemia in renal insufficiency is not known, the following possibilities arise:

Amelioration of diabetes:

That insulin requirement of diabetic patients decreases with age has been known since 1853.[7] Zubrod et al[8] and others,[9,10] have noted a relationship between Kimmelstiel-Wilson lesion with the amelioration of diabetes.

Delayed degradation of insulin:

(a) Renal insulinase: In rats the greatest insulinase activity was present in liver and kidney.[11] It is reasonable to speculate that decrease in this enzyme by malfunctioning kidney might result in delayed degradation of insulin.[12]

(b) Radioisotope studies: Prolongation in the half time in serum of insulin in the presence of renal lesions has been shown in animals[13] and humans.[14] Rabkin et al[15] have shown a decreased uptake of insulin by damaged kidneys. They state this might account for the diminished insulin requirement in patients with diabetic glomerulosclerosis.

Impairment of carbohydrate metabolism in presence of renal disease:

The work of Cohen[16] suggests a deficiency in the hepatic uptake of glucose. This may be due to glycogenolysis and/or gluconeogenesis. Although peripheral resistance to insulin in uremia has been also shown,[17] the possibility of deficiency of recently postulated gluconeogenic pancreatic hormone[18] is an interesting one.

In summary I would like to point out that once a diabetic patient has any evidence of renal disease, his therapy, be it insulin, oral hypoglycemic agent or dietary, should be monitored carefully. An attempt should be made to cut down the hypoglycemic agent in case, especially if the patient is obese, to avoid the vicious cycle of —

Too much insulin on board → Hypoglycemia → Increased food intake → More weight gain → Too much insulin on board → etc.

I have successfully lowered and/or discontinued the hypoglycemic agent in several of these patients.

SOHAN LAL DUA, MB, BS
Sacramento

REFERENCES

1. White MG, Kurtzman NA: Hypoglycemia in diabetes with renal insufficiency. JAMA 215:117, 1971
2. Gutman RA, et al: Failure of high dialysis fluid glucose to prevent the disequilibrium syndrome. Lancet 1:235, 1967
3. Rigg GA, Bercu BA: Hypoglycemia—A complication of hemodialysis. N Engl J Med 277:1139, 1967
4. David DS, et al: Aspirin induced hypoglycemia in a patient on hemodialysis. Lancet 2:1092, 1971
5. Block MB, Rubenstein AH: Spontaneous hypoglycemia in diabetic patients with renal insufficiency. JAMA 213:1863, 1970
6. Greenblatt D: Fatal hypoglycemia after peritoneal dialysis. Br J Med 2:271, 1972
7. Bence Jones H: On intermittent diabetes and on diabetes of old age. Med Chir Tr Roy Med Chir Soc, 1853
8. Zubrod C, Stanton G, Eversole L, et al: Amelioration of diabetic and striking rarity of acidosis in patients with Kimmelstiel-Wilson lesions. N Engl J Med 245:518, 1951
9. Runyan JW Jr, et al: Effect of Kimmelstiel-Wilson syndrome on insulin requirement. N Engl J Med 252:388, 1955
10. Kalliomaki JL, et al: Correlation between insulin requirement and renal retention in diabetic nephropathy. Acta Med Scand 166:423, 1960
11. Mirsky IA, Broh-kahn RH: Inactivation of insulin by tissue extracts, cirstribation and properties of insulin inactivating extracts (insulinase). Arch Biochem 20:1, 1949
12. O'Brien JP, Sharpe AR Jr: Abnormal carbohydrates metabolism in renal failure. Metabolism 14:1294, 1965
13. Ricketts HT, Wildberger HL: Role of the kidney in disposal of insulin in rats. Diabetes 12:155, 1963
14. O'Brien JP, Sharpe AR Jr: The influence of renal disease on the insulin 131-I disappearance curves in man. Metabolism 16: 76, 1967
15. Rabkin R, et al: Effect of renal disease on renal uptake. N Engl J Med 282:182, 1970
16. Cohen BD: Carbohydrate metabolism in renal disease. Blood glucose unresponsiveness to hypoglycemia, epinephrine and glucogon. Ann Int Med 57:204, 1962
17. Hutchings RH, et al: Glucose intolerance in patients on long term intermittent dialysis. Ann Int Med 65:275, 1966
18. Sutton PM, Tazhizadeh A: A new pancreatic hormone and etiology of diabetes mellitus. Lancet 2:935, 1969

Refer to: Jonsen AR: A new ethic for medicine? West J Med 120:169-173, Feb 1974

Special Essay

A New Ethic for Medicine?

ALBERT R. JONSEN, SJ, PhD, *San Francisco*

A NEW ETHIC FOR MEDICINE? Some, physicians and public alike, are calling for a "new ethic." They find medicine's "old ethic" quite unable to deal with the moral problems raised by such medical advances as amniocentesis and artificial means for prolongation of living and dying. Others, physicians and public alike, decry the imminence of a "new ethic" and urge a renewal of vigor of medicine's "old ethic," with its firm stands on such issues as abortion and euthanasia. In the clash of debate over "old" and "new," very little is being said about "ethic." In this article, I shall try to clarify somewhat the meaning of "ethics." I shall then state my agreement with the call for a "new ethic," although I shall define its "newness" in rather different terms than do its usual proponents.

The title of this article is an echo of an editorial which appeared several years ago in the predecessor of this journal [CALIFORNIA MEDICINE 113:67-68, Sep 1970]. The author of the editorial, like other commentators sensitive to the changing mores of medicine and society, predicted that "new demographic, ecological and social realities and aspirations are so powerful that the new ethic of relative rather than absolute and equal values will ultimately prevail as man exercises ever more certain and effective control over his numbers and uses his always comparatively scarce resources to provide the nutrition, housing, economic support, education and health care in such ways as to achieve his desired quality of life and living."

Since the editorial writer's primary example of the substitution of "relative rather than absolute and equal values" was liberalization of medical opinion and of law regarding abortion, his prediction has already begun to be fulfilled. Indeed, the abortion debates of several years ago seem to many, if certainly not to all, to be redolent of past history. We have "progressed" to discussion about genetic engineering and positive euthanasia, the new beginning and end of medical art. However, regardless of the specific issues, the editorial heralded a new concern for "ethics" of medicine and health care. The writer commented that, "since the problems which the new demographic, ecologic and social realities pose are fundamentally biological and ecological in nature and pertain to the survival and well-being of human beings, the participation of physicians and the medical profession will be essential in planning and decision-making at many levels. No other discipline has the knowledge of human nature, human behavior, health and disease, and of what is involved in physical and mental well-being which will be needed."

While I fully agree with the editorialist's principal thesis and with his exhortation for physicians to participate in decision-making, I must respectfully dissent from his assertion that "no other discipline has the knowledge . . . "

I think I have a valid reason for dissent. I am

Dr. Jonsen is adjunct associate professor of Bio-Ethics, University of California, San Francisco, School of Medicine; and formerly was Visiting Scholar, National Library of Medicine, 1973, and President of the University of San Francisco, 1969-1972.

Presented to the Medical Staff, Children's Hospital of the East Bay, Oakland, September 21, 1973.

Submitted November 6, 1973.

Reprint requests to: A. R. Jonsen, SJ, PhD, Health Policy Program, University of California, San Francisco, 1326 Third Avenue, San Francisco, CA 94143.

one of the small, but growing, band of philosophers who have dared move out of our profession's traditional ivory tower into the busy wards and tense operating theaters of the medical center. These are places where every man must prove his skill. The philosopher must demonstrate that he can bring medicine a skill which is plainly and palpably useful. He must show that his own science of philosophy—moral philosophy or ethics in particular—can add to the practice and profession of medicine a dimension which it presently lacks and which it can profitably employ.

What Does an Ethicist Do?

What does an ethicist do? Perhaps it is better to start with what he does not, or ought not, do. First, he is not a prophet, bringing down to benighted mortals tablets graven with moral commandments. He shares with all other mortals those already delivered, by Moses or by the mores, as the case may be. Second, he is not a preacher, exhorting the weak to virtue and the sinner to repentance. He is no better, or worse, at virtue than the rest of men. Finally, he is not a guru, uttering wise solutions to complex problems. He is as confused before complexity as other men. Ethicists no more have a monopoly on morality than physicians have on health.

What then does an ethicist do? He listens to himself and to others argue for or against certain courses of action. So, of course do all men. But he has a professional interest in the forms of argument, in the reasons offered, in the justifications made, in the excuses given. His professional interest has led him to eavesdrop on arguments made throughout history, between Socrates and the Sophists, between the Stoics and the Epicureans, between Aquinas and the Albigensians, between Hobbes and Locke, Hume and Kant, and between many lesser folk who have argued about the right and the wrong action, the good and the bad motive. By listening in on those historical conversations, he has discovered that, while every man has his reasons, the same sorts of reasons keep coming up. Each man, in any particular debate, offers his opinions, his justifications, his excuses; but again and again, similar opinions, justifications, and excuses, keep coming back like an old refrain. This is the stuff of his science: the recognition of constants in variety, the repetition of identical forms amid diversified, individualized instances.

Thus, out of his historical eavesdropping and his present attention, the ethicist forms a theory of moral discourse, in which he tries to account for the patterns. As in the so called "hard" sciences, there are almost as many theories of moral discourse as there are ethicians, but they tend to center or focus around a few "field theories" which unify wide ranges of empirical data. By reference to these theories of ethical discourse, the ethicist undertakes to analyze and to expose the strengths and weaknesses of moral argument. Being neither prophet, nor preacher, nor guru, he can be neither definitive, nor persuasive, nor sagacious. But, by exposing the perennial forms whereby men have argued about the right and the good, he hopes to render present argument more rational, more self-conscious, more articulate. Once this is done, each man must make his own choices.

An ethicist, then, is a scientist of moral discourse. He earns his faculty salary, or is damned to drink the hemlock, by trying to help men argue better about their moral convictions. But what has this to do with medicine? Why an ethicist among the anesthesiologists, cardiologists and otolaryngologists? What have their arguments about medicine to do with morals? I answer with the contention that many, very many, medical arguments are, at bottom, moral arguments; that it is worthwhile to recognize this, and upon recognition it is sensible to bring in a specialist.

Grand Rounds—A Diagnosis in Ethics

As a specialist in moral discourse, I shall presume to hold Grand Rounds, first presenting a case and then offering some generalization about a new ethic for medicine.

The case I shall present illustrates my contention that many a medical judgment is, at bottom, a moral judgment. Admittedly, the case is a rather crass example, but, given the confines of time, I prefer it to more subtle cases which would require longer exposition. I shall, however, after offering my case, suggest several other less obvious areas where hidden moral judgments might be found lurking behind the medical. In teacher's fashion, I shall frustrate and, I hope, stimulate your curiosity by leaving these areas to your own analysis.

In June of this year, the *Washington Post* reported that "more than a third of the welfare mothers who had babies this year at Medicaid expense in Aiken County, South Carolina, have been sterilized under a policy followed by the county's

only three obstetricians. The policy," the *Post* continued, "which doctors said was based on their social views, is that pregnant women on welfare who have as many as three children must agree to be sterilized before the doctors will deliver their babies on Medicaid." Note that the obstetricians quite frankly state that their policy is based "on their social views." However, the article goes on to state that "medical authorities in Aiken county accept the policy as a physician's prerogative." The article quotes Dr. George Poda, chairman of Aiken County Hospital Board of Trustees: "It's not my business to tell another doctor how to practice medicine." Thus, in the eyes of the participants, the decision to sterilize is described variously as "based on social views," "physician's prerogative" and "the practice of medicine."

The ethicist asks a simple question, "What does it mean to say that a physician has a prerogative to practice medicine based upon his social views?"

It is possible to consider this affirmation a "medical judgment," for, while not quite like judgments about hematocrits and bilirubin content, it can be, and often is, supported by an argument about the nature of medicine. It is the nature of medicine to promote the physical and social well-being of people. A physician, committed to good medicine, should be allowed to use his skills as he sees fit in pursuit of this good end. He may and should make judgments about the best means to that end. Thus, he may judge that procreation among welfare recipients should be limited, not only because they are added charges to the welfare budget, but because mothers and children alike suffer physically and psychologically in such a situation. This can reasonably be called a "medical judgment" since it relies on a view of the nature of medicine and its purpose.

However, good medicine, regardless of how good it is, is not, in and of itself, a criterion of morality. Every art, its beneficial purposes and its excellent practice, can be subject to the question, both in general and in particular, "Is it morally right to do this?" The question arises, not because there is any doubt about the worthy motives of the agent or about the expectation of certain benefits, but because whenever anyone decides to confer benefit, his decision may entail, explicitly or implicitly, the imposition of a burden. If that burden is restriction of another's freedom, limitation of another's knowledge, or deprivation of another's human association, then the question raised is the question of morality. In the case at hand, it may be good medicine to ligate fallopian tubes, but is it good morals to ligate freedom? The physical ligation effects a moral ligation which prohibits not merely procreation, but the ability to replace a lost child and the opportunity ever to think of oneself as other than a "welfare recipient," punished by the dominant society.

To say that ligation of freedom, knowledge and association is a moral problem is not to declare that such actions are, prima facie, immoral. It merely locates where the "moral problem" lies. The tradition of western ethics has, almost with unanimity, allowed that "good reasons" can justify such actions. The primary task of ethics is analyzing and assessing the good reasons, the justifications, the excuses, offered.

A "New Ethic" in the Appraisal of Reasons

It is precisely here that we can see the need of a "new ethic" for medicine: We must evaluate the reasons being offered from the point of view of ethics. The new reasons being proposed to justify practices are a brand never previously offered in medicine. For centuries, the healing art brought benefits and burdens to men, but the burdens fell almost exclusively on those who sought the benefit. Bleeding, leeching, dosing and culling all aimed, somewhat randomly, at cure and almost always caused some hurt. But he who sought the benefit would willingly bear the burden. Today, in an increasing number of instances, benefits conferred on some entail some burden laid on others. The equitable distribution of benefits and burdens is a new problem for medicine. It is an old problem for ethics, the problem of justice.

The problem of justice does not appear only in the obvious place, where it has been much discussed, namely the provision of equal access to medical care, the so-called "right" to health care. It also emerges in strange places. The "good practice of medicine" today demands careful experimentation with techniques and drugs before they are widely employed in therapy. But experimentation implies that some within the experimental group will bear the burden of failure, that others may benefit. The problem is most acute when experiments require participation of some who lack the capacity to volunteer. The good practice of medicine demands utmost effort to save life and repair health. However, extraordinary development of intensive care, particularly

neonatal intensive care, salvages many who would have been lost, but might leave many of them badly damaged burdens upon the resources and emotions of those who must care for them. Good medicine creates dramatic and effective life-saving technology, but the exorbitant costs, of dialysis today and of totally implantable artificial hearts tomorrow, siphon scarce resources from primary, preventive and rehabilitative care. Good medicine demands prevention of disease, but today this prevention is no longer limited to quarantine and inoculations. In virtue of amniocentesis and genetic counseling, it can suggest the elimination of carriers of deleterious genes, an elimination which means the cost of restricting the freedom of some and repressing the life of others. A litany of "good medicine" can evoke, again and again, the crucial problem of allocating costs and benefits.

Justice for All

The ancient problem of justice is the intellectual struggle to find the most reasonable and humane way to make such judgment and the political and legal struggle to effect such judgments, once made, in social policy. It is not enough to say that, after adding up benefits and costs, we can maximize one and minimize the other, thus adding to the greater good of the greater number. Justice must ask, "What about the lesser number?" It is not enough to invoke the possibilities of great benefit to others as an excuse for depriving or harming the one. Justice must ask, "Why this one, rather than that one?" The philosopher Leibniz posed the problem most succinctly when he said that justice "requires us to adjust the good we wish to procure for all to the needs and merits of each man."

The editorial writer in California Medicine was rightly troubled by the substitution of a relative for an absolute ethic. The concept of justice, interestingly enough, is neither one nor the other. Its traditional concern has been the reconciliation of absolute and relative. Its absolute precept demands equal treatment for all, which means, as the British philosopher Sidgwick said, "the similar treatment of similars." However, it is clear that this claim for equal treatment issues from men unequal in many respects and out of a variety of situations more dissimilar than similar. Thus a second "relative" precept of justice requires "dissimilar treatment of dissimilars," to quote Sidgwick again. In the light of these two precepts, justice must search for those morally relevant reasons which justify any departure from strictly equal treatment. Traditionally, dissimilarities arising from individual merit and from individual need have been acknowledged as modifying, in certain carefully prescribed ways, the absoluteness of equal treatment. Justice, then, lives in a moral movement between the absolute and the relative.

In a sense, the equality of all men can be called a "common good," for it is a concept applicable to all men in common. Their individual merits and the fulfillment of their individual needs constitute their "private goods." Justice has always recognized the importance of serving the common good and has always been concerned with the problem of preserving the goods of individuals in conjunction with that common good. Medicine, on the other hand, has served the individual good. Only now is it coming to recognize that, in many instances, the service of the individual good may conflict with the common good. This is not a criticism of the physician's practice, either individually or as a group. Many, if not most, physicians are exquisitely sensitive to the human problems of their practice. However, it is crucial that they become aware that what they do and the motives they have, as single responsible persons treating patients, is rigorously limited by the objective conditions of the institution of medicine.

The "Institution of Medicine"

The phrase "institution of medicine" sounds a bit unfamiliar. We are more accustomed to "the practice of medicine" or "the profession of medicine." But modern medicine is not only a practice, the application of skills to single problematic cases. It is not only a profession, the regulation of that practice by science and standards shared by peers. It is an institution, a highly complex interaction of professionals, paraprofessionals and the public, in coordination with a multitude of other institutions, governmental, judicial, commercial, financial, industrial and informational. The practice and the profession are now incorporated into an institution which both creates their potential and imposes their limits. Just as men live by philosophies exhibited in their decisions, so institutions operate by policies exhibited in practice. The basic ethical problems of modern medicine, I contend, lie less in the critical decisions which individual physicians must occasionally make, although morality is ultimately incarnated in the conscientious choices of individuals; they

lie rather in the design of the policies which structure the institution.

For example, the obstetricians' decision to demand sterilization takes place in a policy setting of a federal-state program for medical care. The program is concerned to make medical care available for the indigent. At the same time, it makes possible coercion to effect certain conditions which someone—in this case the physicians, in another an administrator, in yet others, a legislature—deems desirable. It is in such settings that justice, the most public of virtues, becomes relevant, for justice forces inquiry into the fairness, the defensibility and the authority whereby such policy decisions are devised and effected.

Before concluding, I wish to make two points perfectly clear. First, talk of justice evokes for some the looming image of legal regulation of medicine. Medicine has, since Hammurabi etched his tablets, lived uneasily with the law. It is obvious that some legal regulation is indispensible and equally obvious that regulation can be excessive. However, regulation must be not only moderate; it must be just. All justice is not codified into statute, but all statutes must be framed and criticized in the light of justice. Justice in medicine, then, does not mean regulated medicine; it means that whatever of medicine is regulated be justly regulated and that whatever of medicine is not regulated be justly practiced.

Second, to proclaim justice as a new ethic for medicine does not imply an abandonment of the old ethic. It simply calls for its renewal and expansion by the concept of justice. The old ethic for medicine sprung from the virtue of benevolence in the physician and aimed at the creation of a bond of trust between himself and the patient. *Percival's Medical Ethics* of 1804, the first book to bear the title, states in its opening paragraph, "[Physicians] should so study in their deportment so to unite tenderness with steadiness and condescension with authority, as to inspire the minds of their patients with gratitude, respect and confidence."

Benevolence and trust are moral virtues which are intrinsically necessary to the medical relationship. They must be assiduously cultivated, even within the increasingly impersonal forms of medical care. But today, when the medical relationship is surrounded by the machinery of an institution, benevolence and trust must be supplemented by the considerations of justice. The form of the institution must be ethical as well as the hearts of those who work within it.

In conclusion, may I draw your attention to an analogy which sometimes escapes those devoted to the practice of medicine. The invention of the internal combustion engine brought incredible benefits to society. However, we have only recently begun to suspect the costs which those benefits have imposed, costs which are paid by lost environmental beauty and productivity and in ravages within the lungs and upon the highways. The benefits have been built into our way of life; the burdens must in some way be ameliorated. Similarly, medicine has lived in a golden age of science and technology just about as long as the engine has existed. Perhaps it is providential that we have learned to cure, to some extent, the havoc we create. However, the rich benefits of scientific and technological medicine bring their own costs. We are only on the threshold of recognizing them. Because these costs are so often human deprivation and restriction, they must be measured in moral rather than monetary terms. This is the task of the new ethic for medicine, a new task for the ancient and honorable idea of justice.

Refer to: Schneiderman LJ, Prichard L, Fuller S, et al: Birth control, sterilization and abortion—Attitudes of Catholic and Protestant clergymen in San Diego toward use in families with genetic illness (Controversial Ethical Issues). West J Med 120:174-179, Feb 1974

Birth Control, Sterilization and Abortion

Attitudes of Catholic and Protestant Clergymen in San Diego Toward Use in Families with Genetic Illness

LAWRENCE J. SCHNEIDERMAN, MD, LORRAINE PRICHARD, PHN, SCOTT FULLER, MA, *and* LESLIE ATKINSON, BD, MA
La Jolla, California

A questionnaire comprising case histories was administered to 27 Protestant and 27 Catholic clergymen in the San Diego area to test their attitudes toward the use of birth control, sterilization and abortion in families with specific genetic problems. The responses indicated:

- *Catholic and Protestant clergymen do not always follow the official positions of their churches in these matters, although the majority of them do.*
- *Protestant clergymen were more likely to approve of birth control, sterilization, and abortion than Catholic clergymen.*
- *The approval responses of Protestant and Catholic clergymen were not greatly influenced by whether the illness variables involved high Mendelian risk, high psychological cost, high social cost, or poor prognosis.*
- *The approval responses of Protestant and Catholic clergymen were not significantly influenced by the socio-ethnic background of the families.*

BIRTH CONTROL, sterilization and abortion are the most commonly prescribed therapies for genetic illness today. Since they are directed at life itself, rather than at disease, these procedures are not very precise from a medical point of view, and indeed are highly controversial with regard to their moral, ethical and social implications.

Physicians providing genetic counseling to families necessarily discuss therapeutic measures which impinge upon standards of religious belief.[1] It is likely, therefore, that members of the clergy will play an increasingly important role in the management of genetic illness, a field already shared by a variety of non-physician personnel.[2] Our own custom has been to encourage persons to discuss decisions regarding birth control, sterilization and abortion with their clergymen. In the course of this work, we have discovered that clergymen, when confronted with real-life situations, will occasionally take positions at variance with those publicly advocated by their churches.

Because the attitudes of the clergy toward the issues involved in genetic counseling are of direct, practical importance, we elected to explore them in some detail in the San Diego area. In doing so,

From the Departments of Community Medicine and Medicine, University of California, San Diego, School of Medicine, La Jolla; and the Department of Sociology and Office of Religious Affairs, University of California, San Diego.

Reprint requests to: L. J. Schneiderman, MD, Departments of Community Medicine and Medicine, University of California, San Diego, School of Medicine, P.O. Box 109, La Jolla, CA 92037.

however, we chose not to make the customary inquiry into "official positions" or principles espoused in the abstract,[3,4] but rather sought to learn the kinds of recommendations clergymen would make when faced with specific, challenging genetic counseling problems.

In this study we sought to determine:

- The relationship between the religious background of the clergymen and the types of advice given.
- Whether or not illness variables (genetic risk, psychological impact, social cost, prognosis) affected the types of advice given.
- Whether or not the socio-ethnic background of the affected families influenced the types of advice given.

As background we can summarize the current institutional positions of the Catholic and Protestant churches briefly as follows:

The Second Vatican Council in 1962, declared:

> From the moment of its conception, life must be guarded with the greatest care, while abortion and infanticide are horrible crimes.[5]

Pope Paul decreed in his encyclical, *Humanae Vitae,* in 1968:

> Regulating birth is wrong when it involves directly some interruption of the procreative process once begun. The first thing this rules out is all direct abortion, even of a therapeutic kind. The next thing this rules out, as taught so often by the Church, is sterilizing either sex permanently, or for a while. All actions are forbidden which stop the natural effect of any marriage act, whether done before the act or during it, or after it is over.[6]

Within the Protestant Church debate on these matters has intensified over the past five years.[7] Denominations such as the American Baptist, Episcopal, Lutheran, United Church of Christ, United Methodist Church, and Presbyterian Church accept birth control and abortion in certain socioeconomic circumstances. Other groups have rejected this "liberal" trend and allow abortion only in cases of rape and incest, or accept it only under the most life-threatening circumstances to the mother. They include the Church of the Brethren and the National Association of Evangelicals (comprising 39 affiliated denominations, such as the Assemblies of God, Foursquare Gospel, plus local congregations of United Presbyterian, Southern Presbyterian, and American Baptists Conventions, and Disciples of Christ).[8,9]

Methods

Subjects

A letter endorsed by the San Diego Ecumenical Conference was sent to 100 ministers and priests chosen from the parish registry for convenience of location in the San Diego area, informing them of the research project. Following this, an interviewer telephoned recipients of the letter at random to make an appointment to administer the questionnaire in the clergymen's office. A total of 51 Catholic priests were contacted; and of these, 34 agreed to be interviewed.* Of the Protestant ministers 31 were contacted and 27 agreed to be interviewed.† The data presented below were compiled from 27 questionnaires from each group to facilitate comparison. (The 27 Catholic subjects were taken at random from the total of 34.)

Procedures

A trained interviewer with a public health nursing background read the subjects a brief explanatory paragraph followed by a questionnaire describing 24 case histories. These were read to all the subjects in the same order. After each case history, the subject was asked to indicate the modes of therapy he would accept and those he would reject, in the presence or absence of pregnancy. In the absence of pregnancy proposed modes of therapy were:

1. Rhythm method.
2. Birth control medication.
3. Sterilization.

In the presence of pregnancy proposed modes of therapy were:

4. Therapeutic abortion if diagnostic tests proved presence of an affected fetus.
5. Therapeutic abortion despite inability to make a conclusive diagnosis on the fetus.

Interviews took approximately 30 minutes. Responses were tabulated on a separate code sheet to maintain confidentiality, and were analyzed after all the data were collected.

*Of those refusing, 15 gave reasons which suggested they probably would not have taken issue with the official Church position. Two pleaded lack of time.

†Of those refusing, one indicated lack of interest, three pleaded lack of time.

Independent Variables

Genetic illness variables. The case histories were randomized to include combinations of the major variables encountered in typical genetic counseling situations. Each variable appeared the same number of times.

1. *Genetic risk.* Cases involved either a Mendelian risk of 25 percent or greater (for example, cystic fibrosis, galactosemia, neurofibromatosis) or a low empiric risk—2 to 3 percent (for example, Down's syndrome, meningomyelocele, cleft palate).

2. *Psychological impact.* Cases involved severe, long-term psychological consequences (for example, hemophilia, ectodermal dysplasia, muscular dystrophy) or minimal long-term psychological effects (such as color blindness, Pelger-Huet anomaly, tracheo-esophageal fistula).

3. *Social cost.* Cases involved great expense in total medical and institutional care (congenital heart defect, Down's syndrome, cystic fibrosis) or little to no expense (syndactyly, color blindness, spina bifida).

4. *Prognosis.* Cases involved poor life expectancy with or without medical treatment (such as polycystic kidneys, trisomy-D, epidermolysis bullosa) or good life expectancy with or without medical treatment (such as phenylketonuria, cleft palate, hemophilia).

The above variables were chosen in an attempt to see whether the interviewed clergymen discriminated among the various aspects and consequences of genetic illness and whether this discrimination influenced their responses to proposed modes of therapy.

Socio-ethnic Variables

The cases were paired to provide matching genetic illness variables and were written in such a manner that one of the pair described a stereotypical middle class white family, the other a stereotypical lower class non-white family living in the San Diego area. The purpose of this pairing was to test the influence of socio-ethnic factors unrelated to the genetic illness per se.

Case History Examples

Presented below is a matched pair of case histories taken from the questionnaire to illustrate how genetic illness variables and socio-ethnic variables were described. These paired case histories involve high genetic risk, high psychological cost, high social cost with poor prognosis.

Case 2. A young Escondido auto mechanic and his wife have been saving up to buy their own gas station. They learn the sad news that their son is suffering from an incurable form of muscular dystrophy. They take the child at frequent intervals to a neurologist and other specialists, realizing more and more that the child's course will be protracted, leading to an ultimate death, probably of respiratory infection, some time in the teens. This form of muscular dystrophy has a one in four chance of recurring in future offspring. There is no specific cure for the condition and treatment will involve considerable use of a variety of specialty services which will be time-consuming and expensive. What mode of medical care would you approve of or recommend?

Case 22. A Mexican-American truck driver and his wife gave birth to a child with epidermolysis bullosa, a condition characterized by excessively fragile skin which blisters and breaks down to form painful and infected sores. Although children can survive for many years, the severity of the condition often leads to death before adulthood. Treatment consists only of constant attention to the wounds and thus is protracted, painful, and expensive. The father was hoping to save up money to go into business, in which he hoped to be joined some day by his children. Now he considers applying for welfare. The condition has a one in four chance of recurring. What mode of medical care would you approve of or recommend?

Dependent Variables

Approval responses to specific forms of genetic therapy (rhythm method, birth control medication, sterilization, therapeutic abortion with positive diagnosis, therapeutic abortion without diagnosis) in the context of the hypothetical case descriptions by the individual Catholic and Protestant clergymen formed the dependent variables in this study.

Statistical Analysis

Data were analyzed along the following dimensions:

- The relationship of the religious denomination of the interviewed clergymen to approval responses given to specific forms of genetic therapy.
- The relationship of genetic illness variables

to approval responses given to specific forms of genetic therapy.

- The relationship of the apparent socio-ethnic status of the family to approval responses given to specific forms of genetic therapy.
- The relationship between the socio-ethnic variables and the religious denomination of the interviewed clergymen in producing approval responses to a specific form of genetic therapy (that is, is there an interaction effect?).
- The relationship between genetic illness variables and the religious denomination of the interviewed clergymen in producing approval responses to a specific form of genetic therapy (that is, is there an interaction effect?).

TABLE 1.—*Number of Clergymen Approving Therapy Procedures in at Least One Instance (Total of 27 in each category)*

				Therapeutic Abortion	
Clergymen	*Rhythm*	*Birth Control*	*Sterilization*	*With Diagnosis*	*Without Diagnosis*
Protestant ..	27	27	26	23	4
Catholic ...	27	16	5	1	0

Results

Table 1 shows the specific modes of therapy and the number of Protestant and Catholic clergymen indicating approval in response to one or more of the case histories presented in the questionnaire.

Within the Protestant group, 18 out of 19 ministers from the mainline denominations—Methodist, United Church of Christ-Congregational,

TABLE 2.—*The Effect of the Religion of the Subject and Genetic Illness Variables on Approval of Specific Forms of Genetic Therapy**

Forms of Genetic Therapy	*Source of Variation*	*SS*	*DF*	*MS*	*F*
A. Rhythm method	Within group	505	208	2.42	...
	Between groups	71	7	10.14	...
	(a) Genetic illness variable	2	3	.66	NS
	(b) Religion of subject	68	1	68	28.09†
	Interaction	1	3	.33	NS
	TOTAL	576	215		4.19†
B. Birth control	Within group	2,966	208	14	...
	Between groups	2,405	7	344	...
	(a) Genetic illness variable	5	3	2	NS
	(b) Religion of subject	2,394	1	2,394	171 †
	Interaction	6	3	2	NS
	TOTAL	5,371	215		25 †
C. Sterilization	Within group	1,850	208	9.0	...
	Between groups	3,240	7	463	...
	(a) Genetic illness variable	13	3	4	NS
	(b) Religion of subject	3,221	1	3,221	358 †
	Interaction	6	3	2	NS
	TOTAL	5,090	215		51 †
D. Therapeutic abortion with diagnosis	Within group	2,091	208	10	...
	Between groups	1,654	7	236	...
	(a) Genetic illness variable	7	3	2	NS
	(b) Religion of subject	1,639	1	1,639	163.9 †
	Interaction	.....	...	....	NS
	TOTAL	3,745	215		23.6 †
E. Therapeutic abortion without diagnosis*	Within group	809	109	....	...
	Between groups	0	3	....	...
	(a) Genetic illness variable	.....	...	....	NS
	TOTAL	809	107		NS

*A two-way analysis of variance was used in all cases except therapeutic abortion without diagnosis, where a one-way analysis of variance was used. The reason for this is because no Catholic responses were present for therapeutic abortion without diagnosis so only a comparison of genetic illness variables for Protestants was possible. It is assumed that a significant difference exists between Catholic and Protestant clergy on the issue of therapeutic abortion without diagnosis, because there were no Catholic approval responses.

†(F significant at the .01 level)

Key to abbreviations: SS=sum of squares; DF=degree of freedom; MS=mean square; F=F score (see text); NS=not significant.

Lutheran, Presbyterian, Episcopal, and Baptist —approved of therapeutic abortion, while only one Episcopal minister opposed it in all circumstances. Out of the non-mainline denominations—Revival, Christian and Missionary Alliance, Church of the Brethren, Assembly of God, Pentecostal, and Seventh Day Adventists—four out of eight ministers approved of abortion, while the other four opposed it in every genetic counseling situation. Two ministers (Church of the Brethren and Assembly of God) who approved of therapeutic abortion did so in only one instance each.

All the interviewed clergymen accepted in at least one instance the rhythm method as a form of genetic therapy. Although nearly all the Protestant clergymen accepted and nearly all the Catholic clergymen rejected therapeutic abortion in the presence of a positive diagnosis, the difference narrowed sharply with respect to therapeutic abortion in the absence of a definitive diagnosis. Protestant ministers and Catholic priests shared the same trend of declining rates of approval as the forms of genetic therapy became more invasive (that is, from rhythm to contraception to sterilization to abortion).

Table 2 shows the results of the analysis of variance on the effect the religion of subject and genetic illness variables had on approval given to specific forms of genetic therapy. For all forms of genetic therapy the only variable that could account for the difference between groups was the religion of the subject. Protestant ministers gave significantly more approval responses to all forms of genetic therapy than did Catholic priests. Fur-

TABLE 3.—*The Effect of the Religion of the Subject and the Socio-ethnic Status of the Patient on Approval to Specific Forms of Genetic Therapy**

Forms of Genetic Therapy	*Source of Variation*	*SS*	*DF*	*MS*	*F*
A. Rhythm method	Within group	1,301	104	12.5	...
	Between groups	142	3	47.33	...
	(a) Socio-ethnic status	0	1	0	NS
	(b) Religion of subject	135	1	135	10.80†
	Interaction	7	1	7	NS
	TOTAL	1,443	107		3.78†
B. Birth control	Within group	5,466	104	52.55	...
	Between groups	4,961	3	1,654	...
	(a) Socio-ethnic status	11	1	11	NS
	(b) Religion of subject	4,947	1	4,947	94.13†
	Interaction	3	1	3	NS
	TOTAL	10,427	107		31.47†
C. Sterilization	Within group	3,749	104	36	...
	Between groups	6,449	3	2,150	...
	(a) Socio-ethnic status	30	1	30	NS
	(b) Religion of subject	6,410	1	6,410	178 †
	Interaction	9	1	9	NS
	TOTAL	10,198	107		59.72†
D. Therapeutic abortion with diagnosis	Within group	3,851	104	37	...
	Between groups	3,342	3	1,114	...
	(a) Socio-ethnic status	34	1	34	NS
	(b) Religion of subject	3,278	1	3,278	89 †
	Interaction	30	1	30	NS
	TOTAL	7,193	107		30 †
E. Therapeutic abortion without diagnosis*	Within group	1,636	52	0	...
	Between groups	0	1	....	...
	(a) Socio-ethnic status	.....	...	....	NS
	TOTAL	1,636	53		NS

*A two-way analysis of variance was used in all cases except therapeutic abortion without diagnosis, where a one-way analysis of variance was used. The reason for this is because no Catholic responses were present for therapeutic abortion without diagnosis so only a comparison of socio-ethnic variables for Protestants was possible. It is assumed that a significant difference exists between Catholic and Protestant clergy on the issue of therapeutic abortion without diagnosis, because there were no Catholic approval responses.

†(F significant at the .01 level)

Key to abbreviations: SS=sum of squares; DF=degree of freedom; MS=mean square; F=F score (see text); NS=not significant.

thermore, genetic illness variables had no significant influence on the approval of any of the proposed modes of therapy for either the Catholic or Protestant clergymen. There was no interaction effect between the religion of the subject and the genetic illness variables.

Table 3 shows the results of the analysis of variance on the effect the religion of the subject and socio-ethnic status of the patient had on approval given to specific forms of genetic therapy. As occurred in Table 2, the only significant variable was the religion of the clergymen, with Protestants having more approval responses than Catholics. The socio-ethnic status of the families showed no significant effect upon the decisions reached by either Catholic or Protestant clergymen. There was no interaction between the religion of the clergymen and the socio-ethnic status of the family.

Discussion

The Catholic Church has a long and intricate history of debate on the morality of birth control and abortion.[10-12] Recognizing world opinion, it sought to make clear its intentional separation of ethical principles from temporal affairs:

> The Church guards the heritage of God's Word, and draws from it religious and moral principles, without always having at hand a solution to particular problems.[13]

Our observations show that priests, like others who work at the ground level of social welfare, seem sensitive to the personal issues involved with genetic illness when they conflict with abstract laws.

In contrast to the Catholic Church, Protestant statements have tended to show a deliberate effort to bind "moral principles" closely to "particular problems." (For more detailed discussions see Noonan[11] and Curran.[12]) Yet, as this study suggests, there was no observable tendency for interviewed Protestant ministers to be influenced by socio-ethnic factors more than their Catholic colleagues in approving modes of therapy for genetic illness. This study also failed to disclose any relationship of variables associated with the severity of the genetic illness to the likelihood of approving various modes of genetic therapy. In fact for both Catholic and Protestant clergymen, religious beliefs seemed to be the major determinant in decision-making.

The lack of response to illness and socio-ethnic variables may indicate that clergymen do not consider such factors important in weighing these decisions. Yet, since they are so intimately involved in health care it would seem essential that, in the case of genetic illness particularly, more studies and more discussion should take place between health care providers and the clergy.

REFERENCES

1. Fletcher J: *In* Hilton B, Callahan D, Harris M, et al (Eds): Ethical Issues in Human Genetics. New York, Plenum Press, 1973, p 301
2. Clow CL, Reade TM, Scriver CR: Management of hereditary metabolic disease. N Engl J Med 284:1291, 1971
3. Study on Priestly Life and the Ministry, prepared for the National Conference of Catholic Bishops. Washington DC, 1971
4. Hadden JK: The Gathering Storm in the Churches, New York, Doubleday & Co, 1969
5. Abbott WM (Ed): Second Vatican Council (Gaudium et Spes), Sec 51, 1965. The Documents of Vatican II, New York, Herder & Herder, 1966, p 256
6. Hastings A, Horgan J, Keane L, Nowell R (Eds): On Human Life. London, Burns & Oates, 1968, p 128
7. Potter, RB Jr: *In* Cutler DR (Ed): Updating Life and Death (The Abortion Debate): Boston, Beacon Press, 1968
8. Thrapp DL: Los Angeles Times, August 13, 1972, Pt F, p 8
9. Dart J: Los Angeles Times, April 23, 1971, Pt II, p 1
10. Noonan JT: Abortion and the Catholic Church: A Summary History. Nat Law Forum 12:85, 1967
11. Noonan JT: The Morality of Abortion. Cambridge, Harvard University Press, 1970
12. Curran, CE: Contraception: Authority and Dissent. New York, Herder & Herder, 1969
13. Abbott WM (Ed): Second Vatican Council (Gaudium et Spes), Sec 33, 1965, The Documents of Vatican II, New York, Herder & Herder, 1966, p 232

BOOK REVIEWS

CALIFORNIA MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

LICIT AND ILLICIT DRUGS—The Consumers Union Report on Narcotics, Stimulants, Depressants, Inhalants, Hallucinogens, and Marijuana—Including Caffeine, Nicotine and Alcohol—Edward M. Brecher and the Editors of **Consumer Reports**. Little, Brown and Company, 34 Beacon Street, Boston, Mass. (02106), 1972. 623 pages, $3.95 (Paperback).

How would you like to review a book that is two years old; one that you have read on several occasions and which is now sent to you for review after you have recommended it to several students? Such is my task! It's usually a pleasant experience to review a book for a medical journal. The book is often brand new, destined to be a best seller and gives red hot new information. *Licit and Illicit Drugs* is a paperback costing $3.95 which was first published in 1972 but was written in the late 60's. It is clearly a valuable asset to those people interested in the field of drug abuse and alcoholism.

The Consumers Union has been a valuable group evaluating many consumer issues for the average person. In 1963 Consumers Union evaluated *Smoking and the Public Interest* which was very successful. In the late 1960's Edward Brecher, one of the initial participants in Consumers Union's draft on smoking began a study on drug abuse. Mr. Brecher and the editors of *Consumer Reports* spent several years obtaining historical, social, pharmacological, medical and judicial perspectives on the problem of drug abuse and alcoholism. In an inexpensive and easy to read format they prepared a series of facts and opinions concerning legal and illegal drugs. The information on the individual drugs was circulated among forty experts before publication.

This important work stresses the historical and social perspectives on the drugs of abuse as well as the current laws, attitudes, and policies concerning all the commonly used and abused drugs. Their review ended in 1971 and Consumers Union promises to have a continuing update in the pages of *Consumer Reports*. I think most of the data are fairly presented and although some of the attitudes may seem radical, I think they are basically sound. I'm especially impressed with the conclusions concerning the failure of the judicial and penal systems and the skepticism concerning easy solution to these complicated problems. I am also impressed that both sides of many controversial issues are presented. There are an adequate bibliography and index which make the text even more useful.

Clearly the most controversial aspect of the text involves the six major recommendations concerning drug abuse as a whole and the alternatives for dealing with the problems. It would take many pages to discuss the controversies surrounding these proposals, but for anyone interested in the field they make interesting reading. The report is sensible, easy to read, and useful. I recommend the purchase of this text as a format for discussion of these critical issues. If you read it with an open mind you'll clearly enjoy it. It would even make easy reading for parents and teenagers who need a focus for discussion. Try it, you'll like it!

CHARLES E. BECKER, MD

EDITOR'S NOTE: Dr. Becker was asked to review this book at this late date in response to a suggestion from a reader who called it to our attention.

DERMAL PATHOLOGY—Edited by James H. Graham, M.D., Professor of Medicine (Dermatology), Department of Medicine, Chairman, Division of Dermatology, Professor of Pathology, Department of Pathology, Director, Section of Dermal Pathology, University of California, Irvine; Head, Section of Dermatology, Orange County Medical Center, Orange, California; Waine C. Johnson, M.D., Professor of Dermatology, Associate Professor of Pathology, Temple University School of Medicine; Director of Dermal Pathology Laboratory, Skin and Cancer Hospital of Philadelphia, Philadelphia; and Elson B. Helwig, M.D., Chief, Department of Pathology and Branch of Dermal and Gastrointestinal Pathology, Washington, D.C.; Visiting Professor of Pathology in Dermatology, Temple University Health Sciences Center, Philadelphia; Clinical Professor of Pathology (Dermal), George Washington University School of Medicine, Washington, D.C. Harper & Row, Publishers, Medical Department, 2350 Virginia Avenue, Hagerstown, Md. (21740), 1972. 840 pages, 1,155 illustrations, $45.00.

For years the annual post graduate courses in Dermal Pathology held in Philadelphia and elsewhere have been the format of clarifying and expanding knowledge of modern concepts of skin pathology for use by both dermatologists and pathologists. These courses by Graham et al have provided the basis of this textbook supplemented by expansion on many topics and by recent studies by individual authors.

The illustrations are plentiful and are magnificent. The four chapters on histochemistry of the skin, techniques for preparation of skin for histopathologic study and cytodiagnosis of various diseases and tumors exemplify the advanced nature of this text. The remaining thirty-one chapters include basic anatomy, ultrastructive biopsy and gross tissue techniques, basic pathologic changes in skin and their histopathologic features of a large number of cutaneous disorders with emphasis on differential diagnosis both microscopically and clinically. Seven chapters have been authored or co-authored by Elson Helwig and many articles and photographic material credited to the Armed Forces Institute of Pathology are presented.

The classification and illustration of bullous dermatoses are presented in the clearest fashion of any text available. The authors are especially excellent in their discussion of the areas of commonly confused diagnoses such as the premalignant diseases, malignant lymphomas and reactive lymphoid hyperplasia, and palisading and other granulomas. In the lengthy sections on superficial fungus infections there is presented both clinical and histologic material on the wide spectrum of too often overlooked histologic features.

There are several histopathology tests available currently. Pinkus and Mehregan in their *Guide to Dermatohistopathology* provide a clear simple explanation of basic classification and principles. Lever in his *Histopathology of the Skin* attempts to concisely explain clinical and histologic features of every disease. Whereas Graham et al, while not including all cutaneous disorders, offer the clearest explanation of advanced knowledge in all difficult areas of cutaneous pathology in addition to fundamental concepts. This book deserves room on the library shelf of every dermatologist, pathologist, dermatopathologist and resident physicians interested in diagnosis of skin lesions.

LEO INDIANER, MD

in memoriam

Azevedo, John Anthony, Los Altos. Died October 24, 1973 in Davis of pneumonia, aged 79. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1923. Licensed in California in 1923. Doctor Azevedo was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Beal, Philip Gowans, Inglewood. Died October 12, 1973 in Inglewood of hepatic failure, aged 52. Graduate of Cornell University Medical College, New York, 1946. Licensed in California in 1952. Doctor Beal was a member of the Los Angeles County Medical Association.

Biben, Robert Leslie, San Francisco. Died December 4, 1973 in San Francisco, aged 47. Graduate of Hahnemann Medical College and Hospital of Philadelphia, 1948. Licensed in California in 1952. Doctor Biben was a member of the San Francisco Medical Society.

Bristow, David Austin, Fresno. Died December 6, 1973, aged 65. Graduate of University of Southern California School of Medicine, Los Angeles, 1943. Licensed in California in 1943. Doctor Bristow was a member of the Fresno County Medical Society.

Cannon, Lawrence S., Berkeley. Died November 16, 1973 in Berkeley, aged 60. Graduate of the University of Maryland School of Medicine, Baltimore, 1939. Licensed in California in 1947. Doctor Cannon was a member of the Alameda-Contra Costa Medical Association.

Eiler, John Oliver, Bellflower. Died October 30, 1973 in Twenty-Nine Palms of heart disease, aged 78. Graduate of Indiana University School of Medicine, Indianapolis, 1921. Licensed in California in 1923. Doctor Eiler was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Fitzgerald, William J., San Francisco. Died November 21, 1973 at sea, aged 63. Graduate of Long Island College of Medicine, 1936. Licensed in California in 1945. Doctor Fitzgerald was a member of the San Francisco Medical Society.

Geyser, Harry A., Brentwood. Died November 17, 1973 in Pittsburg of heart disease, aged 70. Graduate of the University of St. Aberdeens Faculty of Medicine, Aberdeen, Scotland, 1934. Licensed in California in 1940. Doctor Geyser was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Hartman, Deane Clemens, Los Angeles. Died September 2, 1973 in Los Angeles, aged 64. Graduate of St. Louis University School of Medicine, 1932. Licensed in California in 1943. Doctor Hartman was a member of the Los Angeles County Medical Association.

Kaufman, Bernard, Sr., San Francisco. Died November 18, 1973 in San Francisco, aged 89. Graduate of Cooper Medical College, San Francisco, 1909. Licensed in California in 1909. Doctor Kaufman was a member of the San Francisco Medical Society.

Koppelman, Harold, Beverly Hills. Died October 24, 1973 in Beverly Hills of myocardial infarction, aged 66. Graduate of Columbia University College of Physicians and Surgeons, New York, 1931. Licensed in California in 1941. Doctor Koppelman was a member of the Los Angeles County Medical Association.

MacKay, Eaton MacLeod, Santa Ana. Died October 30, 1973, aged 73. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1926. Licensed in California in 1928. Doctor MacKay was a member of the Orange County Medical Association.

Mankinen, Carl J., Redding. Died November 17, 1973, aged 62. Graduate of the Ohio State University College of Medicine, Columbus, 1934. Licensed in California in 1962. Doctor Mankinen was a member of the Shasta-Trinity County Medical Society.

McClure, Gillian M., Pasadena. Died November 28, 1973 of cancer, aged 43. Graduate of University College Hospital, University of London Faculty of Medicine, London, England, 1954. Licensed in California in 1969. Doctor McClure was a member of the Los Angeles County Medical Association.

Murphy, William Henry, Redwood City. Died November 21, 1973, aged 76. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1924. Licensed in California in 1924. Doctor Murphy was a retired member of the San Mateo County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Olesky, Elmer, Los Angeles. Died November 23, 1973 in Los Angeles of heart disease, aged 71. Graduate of the University of Minnesota Medical School, Minneapolis, 1928. Licensed in California in 1950. Doctor Olesky was an associate member of the Los Angeles County Medical Association.

Page, Warren E., Oakland. Died December 1, 1973 in Santa Rosa of myocardial infarction, aged 73. Graduate of University of Oregon Medical School, Portland, 1927. Licensed in California in 1927. Doctor Page was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

PENDLETON, WALTER R., Long Beach. Died November 18, 1973 in Long Beach of heart disease, aged 74. Graduate of Rush Medical College, Chicago, 1927. Licensed in California in 1927. Doctor Pendleton was a member of the Los Angeles County Medical Association.

RANSOM, CHARLES HERMAN, Garden Grove. Died October 23, 1973 of multiple myeloma, aged 61. Graduate of Washington University School of Medicine, St. Louis, 1941. Licensed in California in 1942. Doctor Ransom was a member of the Orange County Medical Association.

ROOT, HERBERT BLANCHARD, Los Angeles. Died November 16, 1973 in Los Angeles, aged 68. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1931. Licensed in California in 1931. M.D. degree from California College of Medicine, 1962. Doctor Root was a member of the Los Angeles County Medical Association.

SPENCER, FRANK A., Oakland. Died November 28, 1973 in Oakland of cerebral hemorrhage, aged 53. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1946. Licensed in California in 1948. Doctor Spencer was a member of the Alameda-Contra Costa Medical Association.

STAHL, VERNON O., Ontario. Died November 24, 1973 in Loma Linda, aged 70. Graduate of Cornell University Medical College, New York, 1931. Licensed in California in 1933. Doctor Stahl was a member of the San Bernardino County Medical Society.

THOMAS, JOHN MERRILL, Salinas. Died December 6, 1973 in Salinas, aged 42. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1955. Licensed in California in 1956. Doctor Thomas was a member of the Monterey County Medical Society.

WARD, JOHN H., JR., Napa. Died November 24, 1973 in Napa of heart disease, aged 68. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1932. Licensed in California in 1949. Doctor Ward was a member of the Napa County Medical Society.

WERLINICH, MICHAEL, Duarte. Died November 15, 1973, aged 62. Graduate of Medecinski Fakultet Zagregaskog, Universiteta, Zagreb, 1940. Licensed in California in 1947. Doctor Werlinich was a member of the Los Angeles County Medical Association.

Integument!

Our skin—the human integument—covers us, defines us, protects us. But skin is subject to cuts, burns, abrasions. And infections. Neosporin Ointment fights infection by providing broad antibacterial action against susceptible skin invaders. It contains antibiotics that are rarely used systemically, reducing the risk of sensitization.

INDICATIONS: *Therapeutically*, used as an adjunct to appropriate systemic therapy for topical infections, primary or secondary, due to susceptible organisms, as in: • infected burns, skin grafts, surgical incisions, otitis externa • primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis) • traumatic lesions, inflamed or suppurating as a result of bacterial infection.

Prophylactically, the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing.

CONTRAINDICATIONS: Not for use in the external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of the components.

PRECAUTION: As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms and/or fungi. Appropriate measures should be taken if this occurs. Articles in the current medical literature indicate an increase in the prevalence of persons allergic to neomycin. The possibility of such a reaction should be borne in mind.

Complete literature available on request from Professional Services Dept. PML.

NEOSPORIN® Ointment

(POLYMYXIN B-BACITRACIN-NEOMYCIN)

Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5,000 units; zinc bacitracin 400 units; neomycin sulfate 5 mg. (equivalent to 3.5 mg. neomycin base); special white petrolatum q.s. In tubes of 1 oz. and ½ oz. and 1/32 oz. (approx.) foil packets.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

MICROBIOLOGY—Second Edition—Bernard D. Davis, MD, Adele Lehman Professor of Bacterial Physiology, Harvard Medical School; Renato Dulbecco, MD, Assistant Director of Research, Imperial Cancer Research Fund Laboratories, London; Herman N. Eisen, MD, Professor of Immunology, Massachusetts Institute of Technology, Cambridge; Harold S. Ginsberg, MD, Professor and Chairman, Department of Microbiology, College of Physicians and Surgeons, Columbia University, New York; and W. Barry Wood, Jr., MD (deceased), Boury Professor and Director, Department of Microbiology, Johns Hopkins University School of Medicine, Baltimore. Harper & Row, Publishers, Inc., Medical Department, 2350 Virginia Avenue, Hagerstown, MD (21740), 1973. 1584 pages, with 1300 illustrations, $27.50.

MIGRAINE—The Evolution of a Common Disorder—Oliver Sacks, BM, B Ch, Instructor in Neurology, Albert Einstein College of Medicine, New York, Consultant Neurologist, Beth Abraham Hospital, New York. University of California Press, 2223 Fulton Street, Berkeley, CA (94720), 1973, 220 pages, $2.95 (Paperback).

ON WRITING, READING, AND DYSLEXIA—Arthur Linksz, MD, Clinical Professor of Ophthalmology, New York Medical College, Consulting Surgeon, Manhattan Eye, Ear and Throat Hospital, New York City. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 256 pages, $9.75.

PARENTS' GUIDE TO ALLERGY IN CHILDREN—Claude A. Frazier, MD, Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1973. 338 pages, $7.95.

POSTOPERATIVE DISORDERS OF THE GASTROINTESTINAL TRACT—Hastings K. Wright, MD, Chief of General Surgery, Yale-New Haven Hospital, Professor and Chairman, Department of Surgery, Yale University School of Medicine, New Haven; and M. David Tilson, MD, Instructor in Surgery, Yale University School of Medicine. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 204 pages, $14.50.

POWER AND DISSENT IN THE MEDICAL SCHOOL—Samuel W. Bloom, Professor of Sociology and Community Medicine, Mt. Sinai School of Medicine, City University of New York. The Free Press, A Division of Macmillan Publishing Co., Inc., 866 Third Avenue, New York City (10022), 1973. 191 pages, $2.45 (Paperback).

PREVENTING V.D. AND CANCER BY CIRCUMCISION—Abraham Ravich, MD. Philosophical Library, Inc., 15 East 40th Street, New York City (10016), 1973. 211 pages, $9.95.

A PRIMER OF CLINICAL SYMPTOMS—Robert B. Taylor, MD, Harper & Row, Publishers, Medical Department, 2350 Virginia Avenue, Hagerstown, MD (21740), 1973. 220 pages, $10.95.

PROGRESS IN CLINICAL PATHOLOGY—Volume 5—Editor: Mario Stefanini, MD, Abraham Lincoln School of Medicine, University of Illinois, School of the Basic Medical Sciences at Urbana-Champaign, St. Elizabeth Hospital, Danville, Illinois. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 298 pages, $26.00.

PSRO: ORGANIZATION FOR REGIONAL PEER REVIEW—Edited by Barry Decker, MD, Project Director, Arthur D. Little, Inc., Project; and Paul Bonner, MPH, Associate Project Director, Arthur D. Little, Inc., Project. Ballinger Publishing Company, 17 Dunster Street, Cambridge, MA (02138), 1973. 275 pages, $11.50.

THE SOFT FOODS COOKBOOK—Anne S. Chamberlain. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1973. 130 pages, $5.95.

STRESS DISEASE—The Growing Plague—Peter Blythe. St. Martin's Press, 175 Fifth Avenue, New York City (10010), 1973. 175 pages, $1.75.

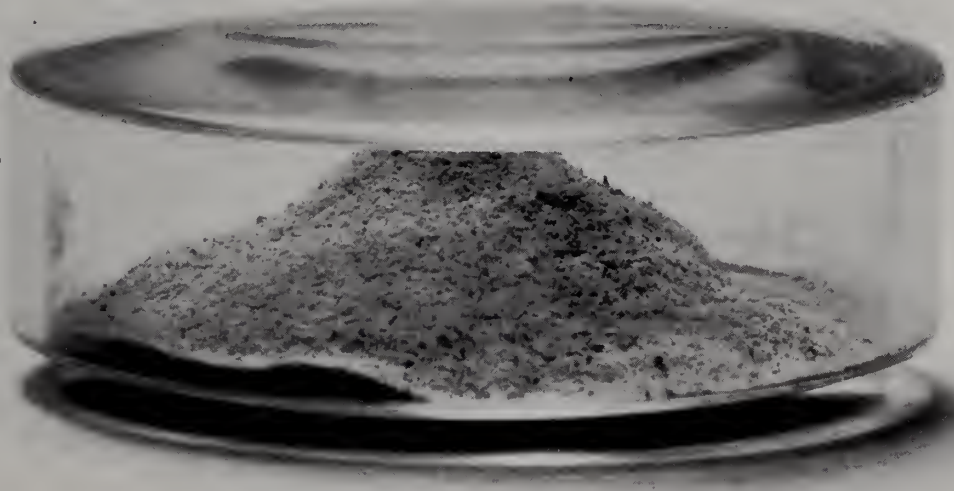
THE STRIATED MUSCLE—Monographs in Pathology—Number 12—Edited by Carl M. Pearson, MD, Professor of Medicine, The University of California, Los Angeles, Center for the Health Sciences; and F. K. Mostofi, MD, Chief, Genitourinary Pathology Branch, Armed Forces Institute of Pathology, and Veterans Administration Special Laboratory for Pathology at the Armed Forces Institute of Pathology, Washington, D.C. The Williams & Wilkins Company, 428 E. Preston St., Baltimore (21202), 1973. 518 pages, $32.00.

SYMPOSIUM ON AESTHETIC SURGERY OF THE NOSE, EARS, AND CHIN—Volume VI—Editors: Frank W. Masters, MD, Professor and Chief, Section of Plastic Surgery, Vice-Chairman, Department of Surgery, University of Kansas Medical Center, Kansas City; John R. Lewis, Jr., MD, Chief, Department of Plastic Surgery, Crawford Long Hospital of Emory University, Chief, Department of Plastic Surgery, Doctors' Memorial Hospital, Atlanta. The C. V. Mosby Company, 3301 Washington Boulevard, St. Louis, MO (63103), 1973. 207 pages, $37.50.

PROLOID® (thyroglobulin)
Caution: Federal law prohibits dispensing without prescription.
Description. Proloid (thyroglobulin) is obtained from a purified extract of frozen hog thyroid. It contains the known calorigenically active components, Sodium Levothyroxine (T_4) and Sodium Liothyronine (T_3). Proloid (thyroglobulin) conforms to the primary USP specifications for desiccated thyroid—for iodine based on chemical assay—and is also biologically assayed and standardized in animals.
Chromatographic analysis to standardize the Sodium Levothyroxine and Sodium Liothyronine content of Proloid (thyroglobulin) is routinely employed.
The ratio of T_4 and T_3 in Proloid (thyroglobulin is approximately 2.5 to 1.
Proloid (thyroglobulin) is stable when stored at usual room temperature.
Indications. Proloid (thyroglobulin) is thyroid replacement therapy for conditions of inadequate endogenous thyroid production: e.g. cretinism and myxedema. Replacement therapy will be effective only in manifestations of hypothyroidism.
In simple (nontoxic) goiter, Proloid (thyroglobulin) may be tried therapeutically, in non-emergency situations, in an attempt to reduce the size of such goiters.
Contraindication. Thyroid preparations are contraindicated in the presence of uncorrected adrenal insufficiency.
Warnings. Thyroglobulin should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 0.5 to 1.0 grain (32 to 64 mg) and increased by the same amount in increments at two-week intervals. This demands careful clinical judgment.
Morphologic hypogonadism and nephrosis should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.
Myxedematous patients are very sensitive to thyroid and dosage should be started at a very low level and increased gradually.
Precaution. As with all thyroid preparations this drug will alter results of thyroid function tests.
Adverse Reactions. Overdosage or too rapid increase in dosage may result in signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac rhythmias, and angina pectoris.
Dosage and Administration. Optimal dosage is usually determined by the patient's clinical response. Confirmatory tests include BMR, ^{131}I resin sponge uptake, T_3 ^{131}I red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Clinical experience has shown that a normal PBI (3.5-8 mcg/100 ml) will be obtained in patients made clinically euthyroid when the content of T_4 and T_3 is adequate. Dosage should be started in small amounts and increased gradually with increments at intervals of one to two weeks. Usual maintenance dose is 0.5 to 3.0 grains (32 to 190 mg) daily.
Overdosage Symptoms. Headache, insomnia, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage may produce the signs and symptoms of hyperthyroidism.
(Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)
How Supplied. ¼ grain; ½ grain; scored ¾ grain; 1½ grain; scored 2 grain; 3 grain; scored 5 grain tablets, in bottles of 100 and 1000.
Full information available on request.
WARNER/CHILCOTT
Division, Warner-Lambert Company
Morris Plains, New Jersey 07950
PR-GP-31-B/W

IN NATURAL THYROID THERAPY:

ARE PATIENTS GETTING THE POTENCY YOU PRESCRIBE?



Unlike U.S.P. desiccated thyroid, Proloid®(thyroglobulin) offers the assurance of constant potency.

To begin with, Proloid is uniquely purified. The thyroglobulin extracted from hog thyroid is devoid of any glandular debris.

Then, Proloid is chemically and biologically assayed to assure consistent metabolic activity from batch to batch. The T_4 and T_3 content of every dose is blended for optimal thyroid replacement.

Important, too, is the fact that Proloid is invariably "fresh" when your patients take it. Under proper storage conditions, its potency will not diminish for at least four years.

All of which adds up to this: the potency of Proloid is constant...for more consistent results.

PROLOID®
(thyroglobulin)

natural thyroid therapy that leaves nothing to chance

(Continued from Page 24)

PRACTICE FOR SALE

GENERAL PSYCHIATRIST retiring from partnership after 27 years private practice in Pasadena area. Goodwill for sale. Salary guarantee. Remaining partner will assist takeover. For details communicate — Bruce Williamson, MD, 2453 Huntington Drive, San Marino, CA 91108; (213) 795-7246.

OFFICES FOR LEASE OR RENT

MODERN MEDICAL SUITE—Cambrian Park area of San Jose; 765-1,600 sq. ft. @ .45. Will consider remodel to suit. Call collect (408) 378-1956.

OFFICES FOR LEASE OR RENT

EUREKA—MEDICAL SUITE AVAILABLE. 1,000 to 1,300 square feet depending on need. New Professional Building adjacent to hospital. Lease available with purchase option. Excellent outdoor recreation area. Hunting, fishing, boating, hiking—you name it. Come and relax on the North Coast, (707) 443-3005.

1,000 SQ. FT. PRIVATE SUITE AVAILABLE in one of 16 custom designed complexes architecturally outstanding medical dental street (28 physicians). Congenial medical community. El Camino district hospital only 2 minutes away. 810 Altos Oaks Drive, Los Altos, CA 94022, phone (415) 948-7070.

MEDICAL EQUIPMENT FOR SALE

GENERAL PRACTICE EQUIPMENT to furnish waiting room, office, EKG, laboratory, and three examining rooms. Used three years, excellent condition, good quality and attractive. Will sell for 40 percent of cost only in one lot—write for detailed list. Western Journal of Medicine, 731 Market Street, Box No. 9374, San Francisco, CA 94103.

FOR SALE—LIFE-PAK 33, Battery operated—portable monitor and defibrillator $1,800, **EKG**—physiocontrol—portable—battery operated $650. Dr. R. Reeve, 975 Sereno Drive, Vallejo, CA 94590, or call (707) 642-6878 or 942-6293.

COMPTON FOUNDATION HOSPITAL

820 West Compton Boulevard
COMPTON, CALIFORNIA 90220
(213) 537-3070
(213) 631-1148

G. CRESWELL BURNS, M.D.
Administrator and Medical Director

HELEN RISLOW BURNS, M.D.
Assistant Medical Director

MEMBER OF
American Hospital Association
and
National Association of Private Psychiatric Hospitals

High Standards of Psychiatric Treatment . . . Serving the Los Angeles Area

Accredited by Joint Commission on Accreditation of Hospitals

YOUR FUNDS COULD BE EARNING 10% INTEREST

Secured by the highest quality trust deeds on prime California real estate with large equities.

You can invest from $2,500 to $100,000 and earn 10% interest per annum from the date of deposit. (And you may receive an additional prepayment bonus of six months' interest as provided for by Section 10242.6 of the California Business and Professions Code.)*

Your investment is fully protected by a policy of title insurance from T.I.&T., fire insurance, and Realty Tax Service. Our Collection Department sends you your checks, and a computerized monthly statement of your account, free of charge.

So, if you want security, simplicity, and an annual yield of at least 10%, contact our Investment Department in person or by phone.

RELIABLE MORTGAGE CORPORATION

320 N. Vermont Ave., L.A.
(213) 666-2525

Trusted and Respected Brokers for 24 Years

*Copies of Section 10242.6 available on request. Offer open to California residents only.

Choloxin®

(sodium dextrothyroxine)

Once-a-day dosage.

See reverse side for full prescribing information and dosage schedule.

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015

Choloxin® (sodium dextrothyroxine)

The Lipid-Lowering Agent with Once-A-Day Dosage

Four strengths . . . 1, 2, 4, and 6 mg. . . . are available making the scored tablet regimen a flexible dosage system. And, for most patients, CHOLOXIN tablets offer once-a-day dosage.

AN IMPORTANT NOTE:
It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CHOLOXIN® (sodium dextrothyroxine) Single-Tablet-A-Day Dosage Schedules

See prescribing information in package insert reproduced below.

	Starting Dosage	Increased by Increments of	Usual Maintenance	Maximal Recommended
Adult Hypercholesterolemic	1.0-2.0 mg.	monthly 1.0-2.0 mg.	4.0-8.0 mg.	4.0-8.0 mg.
Pediatric Hypercholesterolemic	0.05 mg./kg. body weight	monthly 0.05 mg./kg.	0.1 mg./kg. body weight	4.0 mg.
Hypothyroid Cardiac Patients	0.5-1.0 mg.	monthly 1.0 mg.	4.0 mg.	4.0 mg.

Choloxin®
(sodium dextrothyroxine)

Description
CHOLOXIN (sodium dextrothyroxine) is the sodium salt of the dextrorotatory isomer of thyroxine. It is chemically described as O-3,5,3′,5′-tetraiodothyronine sodium salt.

Actions
The predominant effect of CHOLOXIN (sodium dextrothyroxine) is the reduction of serum cholesterol levels in hyperlipidemic patients. Beta lipoprotein and triglyceride fractions may also be reduced from previously elevated levels.

Most of the available evidence indicates that CHOLOXIN stimulates the liver to increase catabolism and excretion of cholesterol and its degradation products via the biliary route into the feces. Cholesterol synthesis is not inhibited and abnormal metabolic end-products do not accumulate in the blood.

Indications
This is not an innocuous drug. Strict attention should be paid to the indications and contraindications.

CHOLOXIN (sodium dextrothyroxine) is an antilipidemic agent used as an adjunct to diet and other measures for the reduction of elevated serum cholesterol (low density lipoproteins) in euthyroid patients with no known evidence of organic heart disease.

The drug is also indicated in the treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

Before prescribing, note the following: Results from a randomized clinical study have indicated a possible adverse effect when CHOLOXIN is administered to a patient receiving a digitalis preparation. There may be an additive effect. This additive effect may possibly stimulate the myocardium excessively in patients with significant myocardial impairment. CHOLOXIN dosage should not exceed 4 mg per day when the patient is receiving a digitalis preparation concomitantly. Careful monitoring of the total effect of both drugs is important.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

Contraindications
The administration of CHOLOXIN (sodium dextrothyroxine) to euthyroid patients with one or more of the following conditions is contraindicated:

1. Known organic heart disease, including angina pectoris; history of myocardial infarction; cardiac arrhythmia or tachycardia, either active or in patients with demonstrated propensity for arrhythmias; rheumatic heart disease; history of congestive heart failure; and decompensated or borderline compensated cardiac status.
2. Hypertensive states (other than mild, labile systolic hypertension).
3. Advanced liver or kidney disease.
4. Pregnancy.
5. Nursing mothers.
6. History of iodism.

Warnings
CHOLOXIN (sodium dextrothyroxine) may potentiate the effects of anticoagulants on prothrombin time. Reductions of anticoagulant dosage by as much as 30% have been required in some patients. Consequently, the dosage of anticoagulants should be reduced by one-third upon initiation of CHOLOXIN therapy and the dosage subsequently readjusted on the basis of prothrombin time. The prothrombin time of patients receiving anticoagulant therapy concomitantly with CHOLOXIN therapy should be observed as frequently as necessary, but at least weekly, during the first few weeks of treatment.

In the surgical patient, it is wise to consider withdrawal of the drug two weeks prior to surgery if the use of anticoagulants during surgery is contemplated.

When CHOLOXIN is used as thyroid replacement therapy in hypothyroid patients with concomitant coronary artery disease (especially those with a history of angina pectoris or myocardial infarction) or other cardiac disease, treatment should be initiated with care. Special consideration of the dosage schedule of CHOLOXIN is required. This drug may increase the oxygen requirements of the myocardium, especially at high dosage levels. Treated subjects with coronary artery disease must be seen at frequent intervals. If aggravation of angina or increased myocardial ischemia, cardiac failure, or clinically significant arrhythmia develops during the treatment of hypothyroid patients, the dosage should be reduced or the drug discontinued.

Special consideration must be given to the dosage of other thyroid medications used concomitantly with CHOLOXIN. As with all thyroactive drugs, hypothyroid patients are more sensitive to a given dose of CHOLOXIN than euthyroid patients.

Epinephrine injection in patients with coronary artery disease may precipitate an episode of coronary insufficiency. This condition may be enhanced in patients receiving thyroid analogues. These phenomena should be kept in mind when catecholamine injections are required in sodium dextrothyroxine-treated patients with coronary artery disease.

Since the possibility of precipitating cardiac arrhythmias during surgery may be greater in patients treated with thyroid hormones, it may be wise to discontinue CHOLOXIN in euthyroid patients at least two weeks prior to an elective operation. During emergency surgery in euthyroid patients, and in surgery in hypothyroid patients in whom it may be advisable to withdraw therapy, the patients should be carefully observed.

There are reports that sodium dextrothyroxine in diabetic patients is capable of increasing blood sugar levels with a resultant increase in requirements of insulin or oral hypoglycemic agents. Special attention should be paid to parameters necessary for good control of the diabetic state in dextrothyroxine-treated subjects and to dosage requirements of insulin or other antidiabetic drugs. If sodium dextrothyroxine is later withdrawn from patients who had required an increase of insulin (or oral hypoglycemic agents) dosage during its administration, the dosage of antidiabetic drugs should be reduced and adjusted to maintain good control of the diabetic state.

When either or both impaired liver or kidney function are present, the advantages of CHOLOXIN therapy must be weighed against the possibility of deleterious results.

Usage in Women of Childbearing Age
Women of childbearing age with familial hypercholesterolemia or hyperlipemia should not be deprived of the use of this drug; it can be given to those patients exercising strict birth control procedures. Since pregnancy may occur despite the use of birth control procedures, administration of CHOLOXIN (sodium dextrothyroxine) to women of this age group should be undertaken only after weighing the possible risk to the fetus against the possible benefits to the mother. Teratogenic studies in two animal species have resulted in no abnormalities in the offspring.

Precautions
It is expected that patients on dextrothyroxine therapy will show greatly increased serum protein-bound-iodine levels. These increased serum PBI values are evidence of absorption and transport of the drug, and should NOT be interpreted as evidence of hypermetabolism; similarly, they may not be used for titrating the effective dose of CHOLOXIN (sodium dextrothyroxine). PBI values in the range of 10 to 25 mcg% in treated patients are common.

If signs or symptoms of iodism develop during CHOLOXIN therapy, the drug should be discontinued.

A few children with familial hypercholesterolemia have been treated with CHOLOXIN for periods of one year or longer with no adverse effects on growth. However, it is recommended that the drug be continued in patients in this age group only if a significant serum cholesterol-lowering effect is observed.

Adverse Reactions
The side effects attributed to dextrothyroxine therapy are, for the most part, due to increased metabolism, and may be minimized by following the recommended dosage schedule. Adverse effects are least commonly seen in euthyroid patients with no signs or symptoms of organic heart disease; the incidence of adverse effects is increased in hypothyroid patients, and is highest in those patients with organic heart disease superimposed on the hypothyroid state.

In the absence of known organic heart disease, some cardiac changes may be precipitated during sodium dextrothyroxine therapy. In addition to angina pectoris, arrhythmia consisting of extrasystoles, ectopic beats, or supraventricular tachycardia, ECG evidence of ischemic myocardial changes and increase in heart size have been observed. Myocardial infarctions, both fatal and non-fatal, have occurred, but these are not unexpected in untreated patients in the age groups studied. It is not known whether any of these infarcts were drug related.

Changes in clinical status that may be related to the metabolic action of the drug include the development of insomnia, nervousness, palpitations, tremors, loss of weight, lid lag, sweating, flushing, hyperthermia, hair loss, diuresis, and menstrual irregularities. Gastrointestinal complaints during therapy have included dyspepsia, nausea and vomiting, constipation, diarrhea, and decrease in appetite.

Other side effects reported to be associated with CHOLOXIN (sodium dextrothyroxine) therapy include the development of headache, changes in libido (increase or decrease), hoarseness, tinnitus, dizziness, peripheral edema, malaise, tiredness, visual disturbances, psychic changes, paresthesia, muscle pain, and various bizarre subjective complaints. Skin rashes, including a few which appeared to be due to iodism, and itching have been attributed to dextrothyroxine by some investigators. Gallstones have been discovered in occasional dextrothyroxine-treated patients and cholestatic jaundice has occurred in one patient, although its relationship to CHOLOXIN therapy was not established.

In several instances, the previously existing conditions of the patient appeared to continue or progress during the administration of CHOLOXIN; a worsening of peripheral vascular disease, sensorium, exophthalmos, and retinopathy have been reported.

CHOLOXIN potentiates the effects of anticoagulants, such as warfarin or Dicumarol, on prothrombin time, thus indicating a decrease in the dosage requirements of the anticoagulants. On the other hand, dosage requirements of antidiabetic drugs have been reported to be increased during dextrothyroxine therapy (see WARNINGS section).

Dosage and Administration
For **adult** euthyroid hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN (sodium dextrothyroxine) is 4 to 8 mg per day. The initial daily dose should be 1 to 2 mg to be increased in 1 to 2 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol.

When used as partial or complete substitution therapy for levothyroxine in hypothyroid patients with cardiac disease who cannot tolerate other types of thyroid medication, the initial daily dose should be 1 mg to be increased in 1 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, preferably the lower dosage. The maximum in patients receiving digitalis therapy is 4 mg.

For **pediatric** hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN is approximately 0.1 mg per kilogram. The initial daily dosage should be approximately 0.05 mg per kilogram to be increased in up to 0.05 mg per kilogram increments at monthly intervals. The recommended maximal dose is 4 mg daily, if that dosage is indicated to effect the desired lowering of serum cholesterol.

If new signs or symptoms of cardiac disease develop during the treatment period, the drug should be withdrawn.

How Supplied
CHOLOXIN (sodium dextrothyroxine) is supplied in prescription packages of scored 1, 2, 4, and 6 mg tablets.

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES INC
Deerfield, Illinois 60015

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine,** Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

ALCOHOLISM AND DRUG USE

April 20-21—**Alcoholism and Drug Abuse: 1974.** UCSF, CMA, Haight-Ashbury Free Medical Clinic, Institute for Social Concerns at UCSF. Saturday-Sunday. $60. Contact: UCSF.

CANCER

February 23—**Newer Developments in Gynecologic Cancer.** UCD. Saturday.

February 27-March 3—**Conference on Oncology—2nd Annual.** UCLA at Riviera Hotel, Palm Springs. Wednesday-Sunday.

March 14-15—**Urology Symposium—Cancer of the Genito-Urinary Tract.** See Surgery, March 14-15.

March 16—**The People Side of Cancer—2nd Annual Rehabilitation Conference.** American Cancer Society, Calif. Division, at Airport Marina Hotel, Los Angeles. Saturday. Contact: Marie Aylward, ACS, Calif. Div., 875 O'Farrell St., San Francisco 94109. (415) 885-5822.

March 21-22—**Clinical Cancer Conference—9th Annual.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday.

Continuously—**Tumor Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. Tuesdays, 4:00 p.m. Contact: Sidney Saltzstein, MD, University Hospital, San Diego. (714) 291-3330, ext. 1071.

Continuously — **Tumor Board — Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Pathology Conference Room, Harbor General Hospital, Torrance. Fridays 3-4 p.m. Advice and consultation from specialists in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: John Benfield, MD, Dept. of Surgery, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 281.

MEDICINE

February 15-17—**Theory and Practice in Echocardiography.** UCLA. Friday-Sunday.

February 20-22—**Current Concepts in the Diagnosis of Pulmonary Disease.** California Thoracic Society at Hyatt on Union Square, San Francisco. Wednesday-Friday. 24 hrs. $125 for members; $150 for non-members. Contact: Elma Plappert, Exec. Secy., CTS, 424 Pendleton Way, Oakland 94621. (415) 636-1756.

February 22—**Myasthenia Gravis.** USC at International Hotel, Palm Springs, Friday.

February 22-23—**Program for Diabetes.** UCD. Friday-Saturday.

February 22-23—**American College of Physicians—20th Southern California Regional Meeting.** Town and Country Hotel, San Diego. Friday-Saturday. 16 hrs. $20 for members; $25 for non-members. Contact: D. R. Tourtellotte, MD, Gen. Chr., 6896 Magnolia Ave., Riverside 92506.

March 1-2—**American College of Physicians—Northern California and Nevada Region.** St. Francis Hotel, San Francisco. Friday-Saturday. $20. Contact: Maurice Fox, MD, Governor, 300 Homer Ave., Palo Alto. (415) 321-4121.

March 4-8—**Arrhythmias Retreat.** USC at Erawan Gardens, Indian Wells. Monday-Friday.

March 11-April 1—**Contra Costa County Heart Association Postgraduate Course.** Sheraton Inn, Concord. Mondays, 8:00 p.m. 8 hrs. $20. Mar. 11—Pulmonary Embolism; Mar. 18—Congestive Heart Failure; Mar. 25—Supraventricular Arrhythmias; Apr. 1—Angina Pectoris. Contact: Mrs. Lois Gustafson, Asst. Dir., 1440 Crokaerts Rd., Walnut Creek. (415) 935-1060.

(Continued on Page 38)

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Arthur Selzer, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.

UCD: University of California, Davis
Contact: George H. Lowery, MD, Professor and Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-3170.

UCI: University of California, California College of Medicine, Irvine
Contact: Donald W. Shafer, MD, Assistant Coordinator, Continuing Medical Education, Regional Medical Programs, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

The Weight of Professional Opinion

It's time for action to defend the laws and regulations that protect your patients against drug substitution.

These professional and trade organizations are united in supporting antisubstitution statutes and regulations:

The American Academy of Dermatology

The Board of Directors of the American Academy of Family Physicians

The Executive Board of the American Academy of Neurology

The Committee on Drugs of the American Academy of Pediatrics

The American College of Allergists

The Executive Committee of the American College of Obstetricians and Gynecologists

The Board of Regents of the American College of Physicians

The Board of Trustees of the American Dental Association

The Board of Trustees of the American Medical Association

The American Psychiatric Association

The Executive Committee of the National Association of Retail Druggists

The Board of Directors of the Pharmaceutical Manufacturers Association

The National Wholesale Druggists' Association

int Statement on Antisubstitution Laws and Regulations

The purpose of this statement is affirm the support of the participat- organizations for the laws, regula- ns and professional traditions which hibit the unauthorized substitution drug products.

Traditionally, physicians, den- ts and pharmacists have worked operatively to serve the best inter- s of patients. Productive coopera- n has been achieved through tual respect as well as a common ncern for the ideals of public vice. This mutual respect has been lected, in part, by joint support r the years for the adoption and orcement of laws and regulations cifically prohibiting unauthorized stitution and encouraging joint cussion and selection of the rce of supply of drug products. basic principles of medical, den- and pharmacy practice are thus ized and preserved in the interest atient welfare.

The antisubstitution laws have obstructed enhancement of the fessional status of pharmacy any re than they have in and of them- es guaranteed absolute protec- from unsafe drugs, or freed sicians, dentists and pharmacists m their responsibilities to patients. practical matter, however, such s and regulations encourage inter- fessional communications regard- drug product selection and assure h profession the opportunity to rcise fully its expertise in drug ge, to the advantage of patients.

Physicians and dentists should rged to increase the frequency regularity of their contacts with rmacists in selection of quality products, recognizing that economies to patients can be im- proved through such communica- tion, taking into account the patients' needs. The pharmacist's knowledge of the chemical characteristics of drugs, their mode of action, toxic properties and other characteristics that assist in making drug selection decisions should be utilized to the fullest extent practicable by physi- cians and dentists in serving their patients.

Since drug product selection entails knowledge derived from clinical experience, the physician's and dentist's roles in product selec- tion remain primary and do not per- mit delegation of decisions requiring medical and dental judgments. A broader role in therapy will evolve for pharmacists as improved under- standing and cooperation among the professions continue to grow.

There has been no evidence that there are convincing reasons to modify or repeal existing laws and regulations prohibiting the unauthor- ized substitution of another drug product for the one specified by a prescriber. It is our belief that such laws and regulations merit the joint support of the medical, dental and pharmaceutical professions and the pharmaceutical industry.

Add your opinion to the weight of other professionals and send it to your state assemblyman or legislator.

P·M·A

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W., Washington, D. C. 20005

At Your Service in The Golden State

In the region named *California* by Spanish adventurers probably after the name of a treasure island in a popular Spanish tale . . .

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY, MISSOURI 64137

is represented by . . .

Dick Bastin

Vito Bell

Mel Bergman

Barry Bialkoski

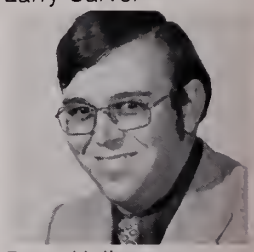
Larry Carver

Dave Evans

Bob Fatch

Richard Foss

Dave Hawks

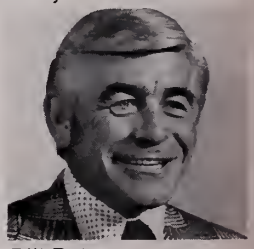

Barry Heilman

Bob Jones

Randy Kennick

Ruth MacKie

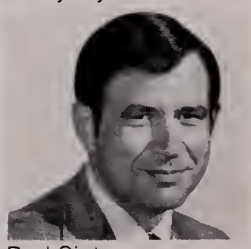
Marty Myers


Bill Palmer

John Patella

Jim Petric

Mike Ryan


Bud Sinkey

Ernie Smith

Bill Stauch

Lorin Waxman

Frank Yannarell

These representatives bring you . . . . . .

Puts comfort in your prescription for nicotinic acid

Description Each capsule contains 400 mg of nicotinic acid in a special base that provides a prolonged systemic affect

Indications NICO-400® is recommended for all disease states in which nicotinic acid has been used. These include conditions associated with deficient circulation and for use in the correction of nicotinic acid deficiencies

Contraindications Individuals with a [illegible] sensitivity to nicotinic acid, severe [illegible] or hemorrhaging

Warnings Use with caution in those patients with history of peptic ulcer, severe diabetes [illegible] bladder or liver functions and [illegible] pregnant women

Adverse Reactions Patients should be [illegible] of the short-lived reactions [illegible] with nicotinic acid therapy [illegible] flushing, a sensation of warmth, [illegible] and itching of the skin, increased [illegible] motility and sebaceous [illegible] activity

Dosage and Administration One capsule [illegible] 12 hours or as directed by physician

Caution Federal law prohibits [illegible] prescription

How Supplied Bottles of 100 [illegible]

Another patient benefit product from

MARION

THE OPTIMAL DOSE, 400-mg, timed-release NICO-400® (nicotinic acid) capsule provides

- Controlled flushing for the desired effects without therapy-limiting side effects.
- Convenient b.i.d. dosage that's less likely to be forgotten.
- The economy of nicotinic acid medication.

For comfort wherever nicotinic acid is used

NICO-400®

(nicotinic acid) Plateau CAPS®

(Continued from Page 33)

March 12—**Dermatology.** USC at Womens Hospital, Los Angeles. Tuesday.

March 13—**Fluid and Electrolyte Workshop.** UCSF at Community Hospital, Santa Cruz. Wednesday.

March 15-16—**Endoscopic Instrumentation and Upper Gastrointestinal Endoscopy.** American Society for Gastrointestinal Endoscopy at Airport Sheraton Hotel, San Diego. Friday-Saturday. 16 hrs. $50 for ASGE members; $75 for nonmembers. Contact: Lee S. Monroe, MD, 476 Prospect St., La Jolla 92037. (714) 459-2390.

March 16—**Clinical Immunology in Medical Practice.** St. Mary Medical Center, Long Beach 90801. (213) 435-4441, ext. 390.

March 19-22—**Consultants' Course in Dermatology.** UCSF. 27 hrs. $150. Tuesday-Friday.

March 20-May 22—**Hematology.** UCLA. 2 months; Wednesdays.

March 25-April 5—**Intensive Review of Internal Medicine.** USC. 2 weeks.

March 29-30—**Cardio-Pulmonary Seminar '74.** Heart Association of the Redwood Empire at Gibson Hall, Solano County Fairgrounds, Vallejo. Friday-Saturday. $35. Contact: Jim Wyatt, Heart Assn. of the Redwood Empire, P.O. Box 844, Santa Rosa 95402. (707) 542-1992.

April 1-10—**Cardiology for the Consultant.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Miss Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, Am. College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

April 3—**Pediatric Nephrology.** See Pediatrics, April 3.

April 3-5—**Diabetes.** UCSF. Wednesday-Friday.

April 4—**Cardiovascular Symposium—20th Annual.** Central Mission Trails Heart Association at Holiday Inn, Santa Cruz. Thursday. Contact: Lynn Putnam, Asst. Dir., 600 S. Main St., Salinas 93901. (408) 424-6007.

April 6—**Arthrography.** UCSF. Saturday.

April 18-19—**Coronary Rehabilitation.** USC. Thursday-Friday.

April 22-26—**Medical Diagnosis and Therapeutics in Internal Medicine.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Friday.

April 24 — **Common Problems in Gastroenterology.** LLU. Wednesday.

Continuously—**Clinical Conferences.** Community Hospital of Santa Cruz. See Of Interest to All, Continuously.

Continuously—**Medical Chest Conference.** St. Mary's Hospital, San Francisco. Tuesdays, 4:00-5:00 p.m. in Pulmonary Classroom. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Medical Morbidity-Mortality Conference.** St. Mary's Hospital, San Francisco. Thursdays, 12:15-1:00 p.m. in Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Clinical Cardiology Conferences.** San Diego County Heart Association at University Hospital, San Diego. Thursdays, 8-10 p.m. Contact: Robert O'Rourke, MD, Instructor, Univ. Hospital, San Diego. (714) 291-3330, ext. 1644. Or Mrs. Cathy Ware, Prog. Dir., San Diego Co. Heart Assn., 3640 5th St., San Diego 92103. (714) 291-7454.

Continuously — **Differential Diagnosis in Internal Medicine.** USC. Fourth Thursday of each month, 7:30-10:00 p.m. September 27, 1973-May 30, 1974.

Continuously—**Renal Dialysis Traineeships.** UCSF. By special arrangement.

Continuously—**Preceptorships in Biochemistry and Biophysics.** UCSF. By arrangement.

Continuously—**Clinics in Dermatology.** UCSF. By arrangement.

Continuously—**Cardiovascular Seminars.** Mondays at 4:30 p.m. in the second floor lecture hall, Basic Science Building, UCSD. Contact: UCSD.

Continuously—**Preceptorships in Cardiology.** American College of Cardiology and PMC. By arrangement. Contact: Arthur Selzer,, MD, PMC; or Miss Mary Anne McInerny, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

Continuously—**Biomedical Lecture Series.** UCSD. Specified Wednesday at 8:00 p.m. For schedule contact UCSD.

Continuously—**Joint Continuing Medical Education Programs for South Bay Hospitals.** UCSD, Bay General Hospital, Chula Vista Community Hospital, Coronado Hospital, Paradise Valley Hospital and CRMP. Programs to be held at various hospitals. Contact: UCSD.

Continuously—**Neurology Conference.** San Joaquin General Hospital, Stockton. Mondays, 10:00-11:30 a.m. in Conference Room 2. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Renal Conference.** San Joaquin General Hospital, Stockton. First Thursday of each month, 11:00 a.m. to 12:00 noon, Conference Room 2. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Wednesday of each month, 10:00-11:30 a.m., Conference Room 1. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Seminar in Clinical and Public Health Aspects of Chest Diseases.** Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Three-hour sessions on second Friday of each month, 9-12 a.m., B-3 classroom, Chest Wards. Presentation of patients demonstrating medical, social, and public health aspects of chest disease, followed by discussion of cases. Course open to physicians, nurses, social workers and personnel concerned with detection and management of patients with chest disease. No fee. Contact: Matthew Locks, MD, Dir., Chest Ward Service, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1245.

Continuously—**Training of Physicians in Modern Concepts of Pulmonary Care.** CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George C. Burton, MD, LLU.

Continuously—**Neurological Sciences.** St. Francis Hospital of Lynwood. Wednesdays, 7:30-8:30 a.m. Presentations of radiological evaluations and pathological specimens of current material and review of current topics in specialty. Weekly notification of cases available. Contact: Ralph Miller, Admin. Asst., St. Francis Hospital of Lynwood, 3620 Imperial Hwy., Lynwood 90262. (213) 639-5111, ext. 365.

Continuously—**Continuing Education in Internal Medicine—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12:00-1:00 p.m. Systematic review of internal medicine, lectures by faculty and visiting professors. Contact: A. James Lewis, MD, Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 647.

Continuously—**Training for Physicians in General Internal Medicine.** CRMP Area VI and LLU at LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

Continuously—**EKG Conference.** St. Francis Hospital of Lynwood, Lynwood. Presented the first Thursday of each month, 12:00-1:30 p.m. A presentation of cases and pathology of recent coronary patients. Contact: Ralph Miller, Admin. Asst., St. Francis Hospital of Lynwood, 3630 Imperial Hwy., Lynwood 90262. (213) 639-5111, ext. 365.

Continuously — **Cardio-angiography Conference.** St. Francis Hospital of Lynwood, Lynwood. Presented the second and fourth Thursday of each month, 12:00-1:30 p.m. Contact: Ralph Miller, Admin. Asst., St. Francis Hospital of Lynwood, 3630 Imperial Hwy., Lynwood 90262. (213) 639-5111, ext. 365.

Continuously—**Basic Home Course in Electrocardiography.** One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. $125 (52 issues). Contact: USC.

Continuously—**Cardiology Conferences — CRMP Area III.** Monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations of local complicated cardiological problems. Contact: William J. Fowkes, Jr., MD, 703 Welch Road, Suite G1, Palo Alto 94304. (415) 321-1200, ext. 6015.

Grand Rounds—Medicine

Tuesdays

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

9:00-10:00 a.m., Morrissey Hall, St. Mary's Hospital, San Francisco.

Neurologist in Chief Rounds. 12:30 p.m., 6 East, University Hospital of San Diego County, San Diego. UCSD.

Wednesdays

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

1st Wednesday of each month, 10:00-11:15 a.m., Conference Room 1, San Joaquin General Hospital, Stockton.

10:30-12 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., University Hospital, UCSD.

12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

Thursdays

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

10:30-12:00 noon, Room 63-105, UCLA Medical Center. UCLA. Second, Third, and Fourth Thursdays.

Neurology. 11:00 a.m., 664 Science, UCSF.

Neurology. 12:30 p.m., University Hospital of San Diego County, San Diego. UCSD.

4th Thursday of each month, 12:30 p.m. in lower conference room, Huntington Intercommunity Hospital, Huntington Beach.

Fridays

8:00 a.m., Auditorium, First Floor, Kern County General Hospital, Bakersfield. UCLA.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. UCLA. Second and Fourth Fridays.

Neurology. 8:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

1st and 3rd Fridays, 8:30 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. UCLA.

Clinicopathologic Conference. 1st Friday, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

Internal Medicine. 2nd, 3rd, and 4th Fridays, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

OBSTETRICS AND GYNECOLOGY

February 23—**New Developments in Gynecologic Cancer.** See Cancer, February 23.

March 14-15—**New Developments in Infectious Disease in Ob/Gyn.** USC. Thursday-Friday.

March 24-25—**Gynecological Laparoscopy: Diagnostic and Operative.** UCI and American Association of Gynecological Laparoscopists at UCI. Sunday-Monday. $100.

April 9-12—**High Risk Pregnancy: Medical and Obstetrical Management.** USC at Gene Autry Hotel, Palm Springs. Tuesday-Friday.

April 10—**Infernal Triangle: Impotence, Infertility, Infections.** LLU. Wednesday.

April 20—**Short Stature Symposium.** See Pediatrics, April 20.

Continuously—**Ob/Gyn Conference.** San Joaquin General Hospital, Stockton. Mondays, 12:00-1:30 p.m. in Doctors' Dining Room. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. See Radiology and Pathology, Continuously.

Grand Rounds—Obstetrics and Gynecology

Mondays

10-11:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Tuesdays

9:00 a.m., Fifth Floor Auditorium, Room 53-105, UCLA Medical Center. UCLA.

Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Center, Sacramento. UCD.

Fridays

8:00 a.m., Auditorium, Orange County Medical Center. UCI.

10:30 a.m., Auditorium, Women's Hospital, Los Angeles County-USC Medical Center, Los Angeles. USC.

Saturdays

8:00 a.m., Executive Dining Room, University Hospital of San Diego County, San Diego. UCSD.

PEDIATRICS

March 7-9—**Oakland's Children's Hospital Medical Center Scientific Meeting.** Sahara Tahoe Hotel, Lake Tahoe. Thursday-Saturday. Contact: Inetta Carty, Children's Hospital Med. Ctr., 51st & Grove Sts., Oakland 94609. (415) 654-5600.

March 7-10—**Combined Southern California Pediatric Postgraduate Meeting—4th Annual.** Los Angeles Pediatric Society; Calif. Chapter 2, American Academy of Pediatrics; Childrens Hospital of L.A.; Childrens Hospital of Orange

County; Southwestern Pediatric Society at Riviera Hotel, Palm Springs. Thursday-Sunday. Contact: L.A. Pediatric Society, P.O. Box 2022, Inglewood 90305. (213) 757-1198.

April 3—**Pediatric Nephrology.** LLU. Wednesday.

April 4-5—**Conference on Management of the Child with Spina Bifida.** STAN and Crippled Children's Service Section, State Dept. of Health at STAN. Thursday-Friday.

April 15-19—**Review of Pediatrics—4th Annual.** USC at Childrens Hospital, Los Angeles. Monday-Friday.

April 20—**Short Stature Symposium.** Division of Medical Genetics, Short Stature Clinic, Harbor General Hospital at Sacramento Inn, Sacramento. Saturday. Contact: Jim Kay, 5748 Straight Way, Carmichael 95608. (916) 445-2627.

Continuously—**Perinatal Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 12:30 p.m., Conference Room. Contact: Marguerite Markarian, MD, Dir. of Nurseries, Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3261.

Continuously—**Pediatric Clinical Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 8:00 a.m., Conference Room "H." Contact: Harry W. Orme, MD, Med. Dir., Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3228.

Continuously—**Preceptorships in Pediatrics.** UCSF. By arrangement.

Continuously—**Pediatric Cardiology Conference.** UCSD, Third Floor Conference Room, University Hospital. Clinical review of cases planned for the week, Tuesdays at 7:30 a.m.; Clinical review of data obtained, Fridays at 1:30 p.m. Contact: UCSD.

Continuously—**Pediatric Research Seminar.** UCSD. Mondays, 12 noon-1:00 p.m.

Continuously—**Pediatrics Clinical Conference.** San Joaquin General Hospital, Stockton. Wednesdays, 10:00-11:15 a.m., Conference Room 3. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric-Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Thursday of each month, 9:30-11:00 a.m., Conference Room 2. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric Cardiology Conference.** St. Vincent's Hospital, Los Angeles. Last Thursday of each month, 12:00 noon, Main floor conference room. Contact: Leonard M. Linde, MD, Chief, Pediatric Cardiology, St. Vincent's Hospital, 3rd and Alvarado Sts., Los Angeles.

Continuously — **Pediatric Conference.** Cedars-Sinai Medical Center, Los Angeles. Thursdays weekly, 8:30-9:30 a.m. Contact: B. M. Kagan, MD, Lebanon Hall, Cedars-Sinai Med. Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 181.

Grand Rounds—Pediatrics

Tuesdays

8:00 a.m., Children's Hospital Medical Center, Oakland.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. UCLA.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

8:30 a.m., University Hospital of San Diego County, San Diego. UCSD.

11:30 a.m., Auditorium, Pediatric Pavilion, Los Angeles County-USC Medical Center, Los Angeles. USC.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Children's Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Children's Hospital, San Francisco.

Thursdays

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA.

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Pediatric Cardiology. 1st Friday of each month. 8:00 a.m., St. Vincent's Hospital, Los Angeles.

8-9:00 a.m., Lecture Hall, Children's Hospital of Los Angeles.

8:30 a.m., Room M104, Stanford University Medical Center, STAN.

8:30-9:30 a.m., alternately at St. Mary's, Children's, Mt. Zion, and Kaiser Hospitals, San Francisco.

9:30-11:00 a.m., Conference Room 2, San Joaquin General Hospital, Stockton.

Infectious Disease. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

PSYCHIATRY

April 3-May 1—**Group Methods.** UCSF at VA Mental Health Clinic, Oakland. One month.

April 8-12—**American Orthopsychiatric Association—51st Annual Meeting.** Hilton Hotel, San Francisco. Monday-Friday. Contact: American Orthopsychiatric Assn., 1775 Broadway, New York 10019. (212) 586-5690.

April 11-14—**Psychiatric Update.** UCLA at Riviera Hotel, Palm Springs. Thursday-Sunday.

Continuously—**Group Methods.** UCSF at VA Mental Health Services, Oakland. January 9-March 13, Wednesdays, 11:30 a.m.-1:00 p.m.

Continuously—**Adolescent Case Review.** St. Mary's Hospital, San Francisco. Wednesdays, 1:00-2:00 p.m., 3 West Conference Room. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Preceptorships in Psychiatry.** UCSF. By arrangement.

Grand Rounds—Psychiatry

Wednesdays

10:30 a.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

11:00 a.m., McAuley Institute, St. Mary's Hospital, San Francisco.

RADIOLOGY AND PATHOLOGY

March 1-8—**American Society of Clinical Pathologists and College of American Pathologists.** Hilton Hotel, Los Angeles. One Week. Contact: Walt Biel, College of American Pathologists, 230 N. Michigan Ave., Chicago 60601.

March 7-10—**Diagnostic Ultrasound.** UCSD at Hotel del Coronado, Coronado. Thursday-Sunday.

(Continued on Page 42)

situation:

.? Washington? London?
the go . . . busy . . . every
ment counts . . .

constipation:

Changing schedules . . . distorted and irregular pattern of eating, sleeping, working . . . tension of travelling . . . result—only too often—constipation.

laxation:

Easy and predictable with one or two SENOKOT Tablets. Taken at bedtime, they usually induce comfortable evacuation in the morning. Leave the traveller free to conduct his business . . . or enjoy his vacation.

Supplied: SENOKOT Tablets (small, easy-to-swallow)—Bottles of 50 and 100, Travel Packs of 16.

Senokot
Tablets
(standardized senna concentrate)

a natural laxative

Purdue Frederick

©COPYRIGHT 1973, THE PURDUE FREDERICK COMPANY/NORWALK CONN. 06856 A7032 128973

(Continued from Page 40)

March 8-9—**Immunopathology of the Nucleic Acids in Rheumatic Diseases.** UCLA. Friday-Saturday.

March 9—**Abnormal Laboratory Data.** PMC. Saturday.

March 9-12—**American Association of Pathologists and Bacteriologists.** Hilton Hotel, San Francisco. Saturday-Tuesday. Contact: Am. Assn. of Pathologists and Bacteriologists, 9650 Rockville Pike, Bethesda, Md. 20014.

March 12-16—**International Academy of Pathology—63rd Annual Meeting.** Hilton Hotel, San Francisco. Tuesday-Saturday. Contact: IAP, 9650 Rockville Pike, Bethesda, Md. 20014.

March 23-24—**Diagnostic Nuclear Imaging: A Review.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

March 25-29—**Diagnostic Radiology—17th Annual Postgraduate Course.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. 33 hrs. $200.

April 13 — **Abnormal Laboratory Data — Thyroid Function Studies.** PMC. 8 hrs. Saturday.

April 26-27—**Laboratory Diagnosis of Immunologic Disorders.** UCSF. Friday-Saturday. 15 hrs. $100.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. Mondays, 12:00 noon, Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Pathology Conference.** St. Mary's Hospital, San Francisco. 2nd and 4th Wednesdays. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Tumor Board.** St. Mary's Hospital, San Francisco. Mondays, 8:00-9:00 a.m., Clinic Building, Room 3. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Clinical Pathology Conference.** St. Mary's Hospital, San Francisco. Third Tuesday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Radiology Film Reading Sessions.** Orange County Radiology Society and Orange County Medical Center at Orange County Medical Center, Orange. 1st Tuesday of each month, September-June, 7:30-9:00 p.m. Contact: Edward J. Miller, MD, 301 Newport Blvd., Newport Beach. (714) 645-8600.

Continuously—**Cytopathology Seminars.** UCSF. 2nd Thursday of each month, September-June. 5:00-6:00 p.m. Contact: Eileen King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously — **Cytopathology Tutorial Program.** UCSF. Courses may be arranged throughout the year on the basis of individual needs and goals; fees are prorated accordingly. Arrangements should be discussed with instructor, Eileen B. King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two-part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

Continuously—**Scintillation Camera Workshop**. UCSF. Workshops provided for physicians and nuclear medicine technologists by special arrangement, limited to 30 trainees per workshop. One- or two-day intensive training periods, basic instruction in scintillation camera theory, scintographic principles and scintiphotographic interpretations. $50. Contact: UCSF.

Continuously — **Scintiphotograph Interpretation.** UCSF and Nuclear Medicine Section, Department of Radiology, UCSF. By special arrangement, designed to furnish physicians with an opportunity to participate in the daily activities of a university laboratory. Two-week training period participation in daily interpretation conferences, correlation conferences, routine training conferences. $175. Contact: UCSF.

Grand Rounds—Radiology-Pathology

Mondays

Pathology. 1:00 p.m., Sacramento Medical Center, Sacramento. UCD.

Tuesdays

Radiology. 3rd Tuesday of each month, 8:00 a.m., Bothin Auditorium, Children's Hospital and Adult Medical Center, San Francisco.

SURGERY AND ANESTHESIOLOGY

February 15—**Problems of the Hip in Children.** American Academy of Orthopaedic Surgeons at Biltmore Hotel, Santa Barbara. Friday. Contact: Dean A. Smith, MD, P.O. Box 1200, Santa Barbara 93102.

February 16—**Postgraduate Refresher Course—Orthopaedic Surgery and Surgical Anatomy of Wrist and Hand.** International College of Surgeons, So. Calif. Division, at Los Angeles Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Darline Murphy, Ex. Sec., ICS, So. Calif. Div., 136 N. Brighton, Burbank 91506. (213) 846-0669.

February 17-March 1—**Temporal Bone Surgical Dissection Course.** Los Angeles Foundation of Otology, Los Angeles. 13 days. $1,000; $750 for residents. Contact: Jack L. Pulec, MD, L.A. Foundation of Otology, 2130 W. 3rd St., Los Angeles 90057.

February 20-22—**Critical Care Medicine and Circulatory Shock.** See Of Interest to All, February 20-22.

February 22—**Myasthenia Gravis.** See Medicine, February 22.

March 3—**Neuro-Ophthalmology Symposium.** CMA Ophthalmology Section at Hilton Hotel, San Francisco. Sunday. 7 hrs. $15 (includes lunch). Contact: Robert E. Christensen, MD, 800 Westwood Plaza, Los Angeles 90024.

March 7-9—**Advances in Vitreous Surgery.** UCSF. Thursday-Saturday.

March 7-10—**Western Orthopedic Association, Northern California Branch.** Ahwahnee Hotel, Yosemite National Park. Thursday-Sunday. Contact: Ida Ruth Haggerty, Exec. Secy., 145 Kimberlin Heights Dr., Oakland 94619.

March 14-15—**Urology Symposium—Cancer of the Genito-Urinary Tract.** STAN. Thursday-Friday.

March 16—**Postgraduate Refresher Course—Surgery and Surgical Anatomy of the Head and Neck.** International College of Surgeons, So. Calif. Division, at Los Angeles Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Darline Murphy, Ex. Sec., ICS, So. Calif. Div., 136 N. Brighton, Burbank 91506. (213) 846-0669.

March 16-17—**Los Angeles County Society of Anesthesiologists —XIX Postgraduate Assembly.** Hilton Hotel, Los Angeles. Saturday-Sunday. 15 hrs. $50 for members; $60 non-members; $50 military; $20 students, residents, interns. Contact: Virginia Connor, Exec. Secy., LACSA, 184 N. Canon Dr., Beverly Hills 90210. (213) 275-4315.

March 16-17—**Low Back Pain.** UCLA. Saturday-Sunday.

March 17-29—**Temporal Bone Surgical Dissection Course.** Los Angeles Foundation of Otology, Los Angeles. 13 days. $1,000; $750 for residents. Contact: Jack L. Pulec, MD, L.A. Foundation of Otology, 2130 W. 3rd St., L.A. 90057.

March 18-20—**G. Mosser Taylor Course in Orthopedic Surgical Anatomy—Spine.** LLU. Monday-Wednesday.

March 20-23—**Conference on Management of Trauma.** UCLA at Riviera Hotel, Palm Springs. Wednesday-Saturday.

March 23-27—**Conference on Controversial Areas in Surgery.** UCLA at Riviera Hotel, Palm Springs. Saturday-Wednesday.

March 28-30—**General Surgery.** UCSF at Hilton Hotel, San Francisco, Thursday-Saturday.

April 7-19—**Temporal Bone Surgical Dissection Course.** Los Angeles Foundation of Otology. 13 days. $1,000; $750 for residents. Contact: Jack L. Pulec, MD, L.A. Foundation of Otology, 2130 W. 3rd St., L.A. 90057.

April 10—**Management of Acute Trauma.** UCSF at Community Hospital, Santa Cruz. Wednesday.

April 17-21—**Vascular Surgery—2nd Annual.** UCLA at Riviera Hotel, Palm Springs. Wednesday-Sunday.

April 20—**Surgical Anatomy and Surgery of the Abdomen.** International College of Surgeons, Southern Calif. Division, at Los Angeles Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Darline Murphy, Ex. Sec., ICS, So. Calif. Div., 136 N. Brighton, Burbank 91506. (213) 846-0669.

April 28-May 5—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

Continuously—**Basic Science Lecture Series.** Dept. of Surgery, St. Mary's Hospital, San Francisco. Mondays, 11:15 a.m.-12:15 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Mini Residencies in Orthopaedics.** STAN. Postgraduate traineeships of 4-14 days duration, as you wish. No tuition but donations accepted. Contact: Orthopaedic Division, Dept. of Surgery, Stanford.

Continuously—**Orthopedic Lecture Series.** Alternately at St. Mary's, St. Joseph's, Mary's Help, VA Martinez, Kaiser San Francisco, and Harkness Memorial Hospitals. Third Tuesday of each month, 6:00 p.m. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Orthopedic Trauma Conference.** USC at Los Angeles County-USC Medical Center. Mondays, 7:00-9:00 p.m. Contact: Dept. of Orthopedics, USC School of Med., 2025 Zonal Ave., Los Angeles 90033. (213) 225-3131.

Continuously—**Preceptorships in General Surgery.** UCSF. By arrangement.

Continuously—**Preceptorships in Neurological Surgery.** UCSF. By arrangement.

Continuously—**Preceptorships in Urology.** UCSF. By arrangement.

Continuously—**Training for Physicians in Nephrology.** CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Stewart W. Shankel, MD, LLU.

Continuously—**Surgical Anatomy.** St. Mary's Hospital, San Francisco. Mondays, 4:30 p.m., St. Mary's Hall, 2 W. Classroom. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Cline Clinic.** St. Mary's Hospital, San Francisco. Mondays, 1:30 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Morbidity and Mortality Conference.** 4th Monday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Surgical Pathology Conference.** See Radiology/Pathology, Continuously.

Continuously—**Thoracic Surgery Conference.** San Joaquin General Hospital, Stockton. Fourth Wednesday of each month, 9:00-10:30 a.m., Conference Room 1. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Medical Surgical Combined Conference.** San Joaquin General Hospital, Stockton. Second Wednesday of each month, 10:00-11:15 a.m., Conference Room 1. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Orthopaedic Audio-Synopsis Foundation.** A nonprofit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Twelve monthly c-60 cassette tapes. Annual subscription rate $72 ($36 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

Grand Rounds—Surgery

Mondays

9-10 a.m., Morrissey Hall, St. Mary's Hosiptal, San Francisco.

Tuesdays

Orthopedic Surgery. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:00-10:00 a.m., San Joaquin General Hospital, Stockton.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. UCLA.

3:30 p.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

Neurology and **Neurosurgery.** 11:00-12:15, Room 663, Science Building, UCSF.

Fridays

1:00-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego, UCSD.

Urology. 8:00 a.m., 3rd floor conference room, University Hospital of San Diego County, San Diego. UCSD.

Orthopedics. 8:00-9:00 a.m. St. Mary's Hospital, San Francisco.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA.

Orthopedics. 10:00 a.m. Auditorium of the Children's Division, Los Angeles County-USC Medical Center. The third Saturday of each month. USC.

OF INTEREST TO ALL PHYSICIANS

February 16—**Zoonotic Diseases Transmitted Between Animal and Man.** UCLA. Saturday.

February 16—**Medical Audit/PSRO.** UCLA. Saturday.

February 16—**Postgraduate Refresher Course — Orthopaedic Surgery and Surgical Anatomy of Wrist and Hand.** See Surgery, February 16.

February 18-23—**Family Practice Review.** UCI at Newporter Inn, Newport Beach. Monday-Saturday. Contact: Chuck Paul, University Extension, 424-B Computer Science Bldg., UCI, Irvine 92664.

February 20-22—**Critical Care Medicine and Circulatory Shock.** USC at Disneyland Hotel, Anaheim. Wednesday-Friday.

February 23-27—**LLU Alumni Postgraduate Convention.** Saturday-Wednesday. Contact: Wilfred J. Snodgrass, MD, Gen. Chr., 1832 Michigan Ave., Los Angeles 90033. (213) 262-2173.

February 25-March 1—**Basic Science for Clinicians—Interdepartmental Course.** STAN. Monday-Friday.

March 1—**Obesity.** USC. Friday.

March 2—**Utilization Review in Hospital Patients.** UCSF at St. Francis Hospital, San Francisco. Saturday.

March 2-6—**California Medical Association—103rd Annual Session.** Hilton Hotel, San Francisco. Saturday-Wednesday.

March 13—**New Techniques in the Care of the Critically Ill.** USC. Wednesday.

March 16—**Postgraduate Refresher Course—Surgery and Surgical Anatomy of the Head and Neck.** See Surgery, March 16.

March 16—**Psychiatry for GPs.** UCSF at Napa State Hospital, Imola. Saturday.

March 16—**Clinical Immunology in Medical Practice.** See Medicine, March 16.

March 16-17—**Human Sexuality and the Health Professional.** UCLA. Saturday-Sunday. $50.

March 29—**Organizing and Conducting Committees.** PMC. Friday. For directors of medical education.

March 30—**Urologic Problems in General Practice.** UCD. Saturday.

April 1-May 27—**Problem Oriented Medical Records.** UCLA. 8 weeks, Monday evenings.

April 4-5—**West Coast Counties Regional Postgraduate Institute.** California Medical Association at Del Monte Hyatt House, Monterey. Thursday-Friday. Contact: Richard Manley, CMA.

April 5-6—**Thy Brother's Keeper.** USC. Friday-Saturday.

April 10—**The Infernal Triangle: Impotence, Infertility, Infections.** See Obstetrics and Gynecology, April 10.

April 16-18—**Family Practitioners: Heart Oriented Clinical Office Practice.** UCLA. Tuesday-Thursday.

April 19-20—**Conference on Physical Fitness and Sports Medicine.** California Medical Association at Hilton Inn, San Diego. Friday-Saturday. Contact: Richard Manley, CMA.

April 20—**Short Stature Symposium.** See Pediatrics, April 20.

April 22-28—**An Introduction to Diving Medicine.** UCSF at VA Hospital, Fresno. Wednesday-Sunday.

April 26—**Educational Methodology I—Simulation and Video.** PMC. Friday. For directors of medical education.

Continuously—**Clinical Conferences.** UCSF and Community Hospital of Santa Cruz at Community Hospital, Santa Cruz. 2nd Wednesday of each month, Oct. 10, 1973-June 12, 1974, 11:00 a.m.-2:30 p.m. 27 hours. $50 for series; $7.50 per lecture. Feb.—A Clinic on Thyroid Disease; Mar.—Fluid and Electrolyte Workshop; Apr.—Management of Acute Trauma; May—Clinic on Obesity; June—The Impotent Male and the Liberated Female.

Continuously—**Emergency Medicine.** USC. Wednesdays, 7:30-9:30 p.m.

Continuously—**Bedside Clinics.** See Medicine, Continuously.

Continuously—**Family Health Program—Southern California.** 2925 N. Palo Verde, Long Beach. Second Friday of each month. 1:00-2:00 p.m. Contact: UCI.

Continuously — **Lecture Program.** Riverside-San Bernardino Chapter, American Academy of Family Physicians and UCI at Ram's Horn Inn, San Bernardino. 3rd Thursday of each month. 7:30 p.m. Contact: UCI.

Continuously—**Lecture Program.** UCI and Orange County Chapter, American Academy of Family Physicians at Saddleback Inn, Santa Ana. 2nd Monday of each month, 7:30 p.m. Contact: UCI.

Continuously—**Hospital Lecture Program.** UCI at Anaheim Mem. Hosp.; Brea Comm. Hosp.; Fountain Valley Comm. Hosp.; Garden Park Gen. Hosp., Anaheim; Hartland Comm. Hosp., Baldwin Park; Huntington Intercomm. Hosp., Huntington Beach; Imperial Gen. Hosp., Inglewood; La Habra Comm. Hosp.; La Mirada Comm. Hosp.; Los Alamitos Gen. Hosp.; Mission Comm. Hosp., Mission Viejo; Palm Harbor Hosp., Garden Grove; Rio Hondo Mem. Hosp., Downey; San Gabriel Valley Comm. Hosp., San Gabriel; Stanton Comm. Hosp.; Studebaker Comm. Hosp., Norwalk; West Anaheim Gen. Hosp.; Westminster Comm. Hosp. Contact: UCI.

Continuously—**Professional Education Program.** Porterville State Hospital. Contact: Frank McCarry, MD, P.O. Box 2000, Porterville. (209) 784-2000.

Continuously—**Round Tables with Pacific Medical Center.** PMC and Sonoma Valley Hospital at Sonoma Valley Hospital, Sonoma. Second Monday of each month in Dining Room of the hospital, 8:00-10:00 p.m. $100 per series, $15 per session. Contact: William J. Newman, MD, P.O. Box B, Sonoma 95476. (707) 996-3621.

Continuously—**Basic Science Lecture Series.** UCSD Mondays, 4:00 p.m., third floor conference room, University Hospital of San Diego County, San Diego. Contact: UCSD.

Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $75 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

Continuously—**Medical Media Network.** Programs and study guides produced in association with faculties of major medical schools and centers throughout California. MMN administered by University Extension, UCLA. Subscriptions for all California hospitals, rental or purchase, 16 mm, super 8 mm, one-inch videotape. Provides physicians throughout the state with current educational programs in local hospitals. Consult the nearest MMN Hospital regarding time and date for viewing. Contact: Mr. David E. Caldwell, Exec. Dir., MMN, 10995 Le Conte Ave., Los Angeles 90024. (213) 825-1791.

Continuously—**Stanford Speaker's Bureau for Environmental Topics.** Stanford University Committee for Environmental Information. Provides on request speakers and programs on environmental topics. Air pollution, water pollution and water conservation issues, radiation hazards and radiation technology, pesticides and their ecological problems, medicine's responsibilities in the environmental-ecology crisis and others. Contact: STAN.

Continuously—**Stanford-Mills Memorial Hospital Continuing Education Program.** STAN at Mills Memorial Hospital, San Mateo. Tuesday-Friday weekly. Basic Science for the Clinician, Grand Rounds, Intensive Care. Contact: STAN.

(Continued on Page 46)

Sign of a cold sufferer

Time for Ornade®

Each capsule contains 8 mg. Teldrin® (brand of chlorpheniramine maleate); 50 mg. phenylpropanolamine hydrochloride; 2.5 mg. isopropamide, as the iodide.

Fast relief of upper respiratory congestion and hypersecretion with convenient b.i.d. dosage.

Before prescribing, see complete prescribing information in SK&F literature or *PDR*.

Indications: Upper respiratory congestion and hypersecretion associated with: the common cold; acute and chronic sinusitis; vasomotor rhinitis; allergic rhinitis (hay fever, "rose fever," etc.).

Contraindications: Hypersensitivity to any component; concurrent MAO inhibitor therapy; severe hypertension; bronchial asthma; coronary artery disease; stenosing peptic ulcer; pyloroduodenal or bladder neck obstruction. Children under 6.

Warnings: Caution patients about activities requiring alertness (e.g., operating vehicles or machinery). Warn patients of possible additive effects with alcohol and other CNS depressants.

Usage in Pregnancy: In pregnancy, nursing mothers and women who might bear children, weigh potential benefits against hazards. Inhibition of lactation may occur.

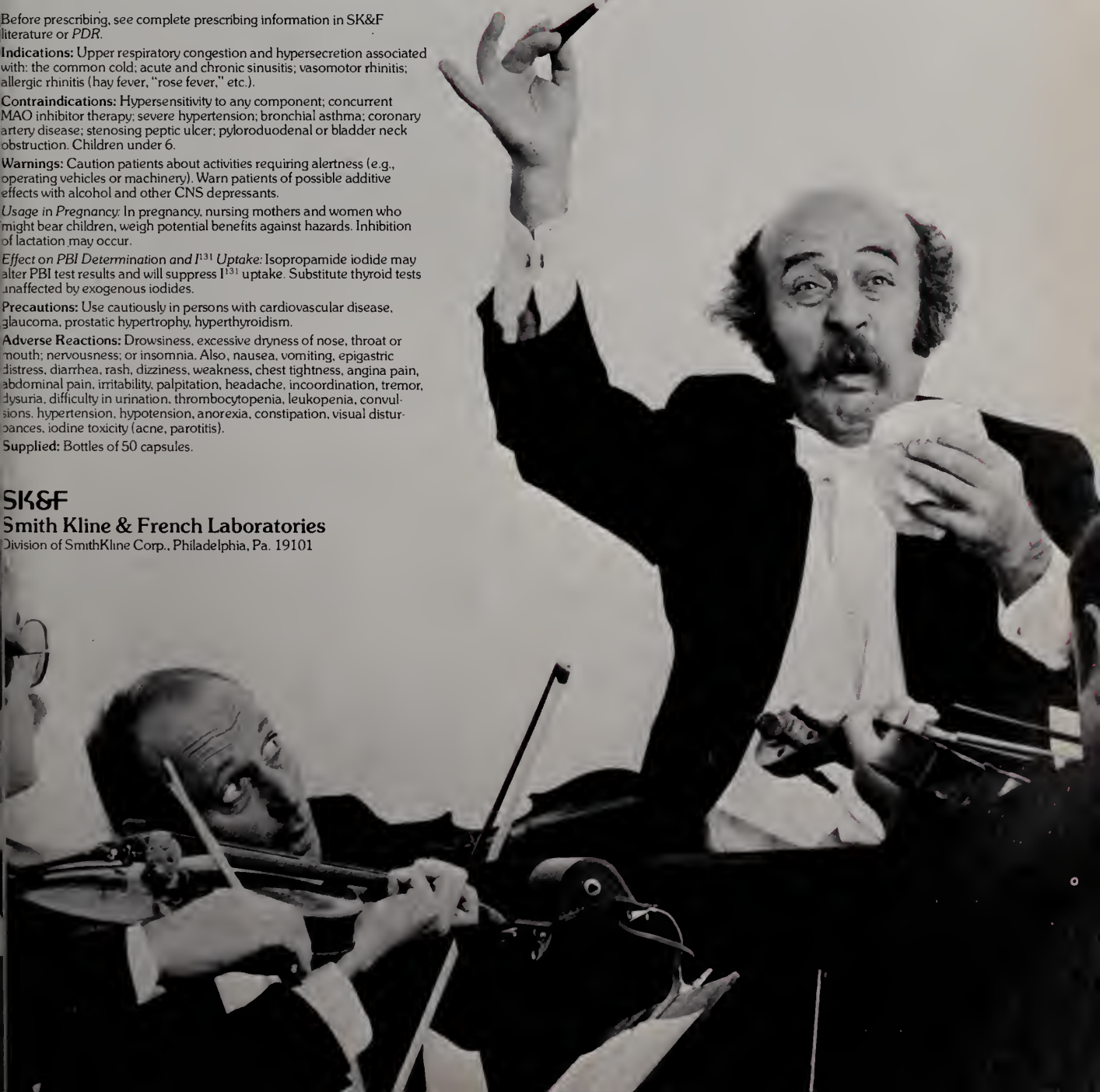
Effect on PBI Determination and I^{131} Uptake: Isopropamide iodide may alter PBI test results and will suppress I^{131} uptake. Substitute thyroid tests unaffected by exogenous iodides.

Precautions: Use cautiously in persons with cardiovascular disease, glaucoma, prostatic hypertrophy, hyperthyroidism.

Adverse Reactions: Drowsiness, excessive dryness of nose, throat or mouth; nervousness; or insomnia. Also, nausea, vomiting, epigastric distress, diarrhea, rash, dizziness, weakness, chest tightness, angina pain, abdominal pain, irritability, palpitation, headache, incoordination, tremor, dysuria, difficulty in urination, thrombocytopenia, leukopenia, convulsions, hypertension, hypotension, anorexia, constipation, visual disturbances, iodine toxicity (acne, parotitis).

Supplied: Bottles of 50 capsules.

SK&F
Smith Kline & French Laboratories
Division of SmithKline Corp., Philadelphia, Pa. 19101



(Continued from Page 44)

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

FAMILY PRACTICE

April 17-19—**Sommer Memorial Lectures.** Benson Hotel, Portland.

MEDICINE

February 27 and 28—**Traumatic Emergencies.** Newport and Coos Bay. Contact: Circuit Course Program, Oregon Medical Association. 4 Credits OAFP and OMA. Tuition $20.

April 24—**Traumatic Emergencies.** Corvallis. Contact: Circuit Course Program, Oregon Medical Association. 4 Credits OAFP and OMA. Tuition $20.

May 15-17—**Combined American College of Emergency Physicians, Emergency Department Nurses Association, and Emergency Medical Technicians.** Contact: Donald L. McNeill, MD, Good Samaritan Hospital, 1015 N.W. 22nd, Portland 97210.

OBSTETRICS AND PEDIATRICS

February 20, 21 and 22—**Pediatric and Ob Emergencies.** Klamath Falls, Medford and Roseburg. Contact: Circuit Course Program, Oregon Medical Association. 4 Credits OAFP and OMA. Tuition $20.

April 10 and 11—**Pediatric and Ob Emergencies.** Eugene and Bend. Contact: Circuit Course Program, Oregon Medical Association. 4 Credits OAFP and OMA. Tuition $20.

SURGERY

February 14-16—**Chest Disease Conference.** Gleneden Beach, Salishan. Contact: Oregon Thoracic Society, 1020 S.W. Taylor Street, Portland.

March 6—**Medical and Surgical Emergencies.** Salem. Contact: Circuit Course Program, Oregon Medical Association. 4 Credits OAFP and OMA. Tuition $20.

April 3 and 4—**Medical and Surgical Emergencies.** Pendleton and LaGrande. Contact: Circuit Course Program, Oregon Medical Association. 4 Credits OAFP and OMA. Tuition $20.

MEDICAL GRAND ROUNDS

March 6—8:00 a.m.—Providence Hospital, Portland—Parenteral Hyperalimentation.

March 12—7:00 p.m.—Providence Hospital, Portland—Management and Mismanagement of the Patient with Chronic Pain.

April 2—7:00 p.m.—Providence Hospital, Portland—The Clinical Significance of Bile Salt Metabolism.

April 11—5:00 p.m.—Providence Hospital, Portland—Depression Symposium.

April 24—8:00 a.m.—Providence Hospital, Portland—Multi-Element Echocardiography.

May 21—7:00 p.m.—Providence Hospital, Portland—Consequences and Cures of the Use of Prescription Drugs.

OF INTEREST TO ALL PHYSICIANS

April 5-7—**Oregon Medical Association Mid-Year Meeting.** Inn at Otter Crest at Otter Rock, Oregon. Contact: J. A. Kronenberg, Associate Executive Director, Oregon Medical Association, 2164 S.W. Park Place, Portland 97205.

WASHINGTON, MONTANA and ALASKA

REGIONAL MEDICAL PROGRAM

THIS LISTING of continuing medical education activities in Washington, Montana, and Alaska is supplied by Washington/Alaska Regional Medical Program. In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Communications Specialist, RMP, 500 University District Building, Seattle, Washington 98105.

February 21-22—**Human Sexuality Counseling Workshop.** UW at Olympic Hotel, Seattle. Thursday-Friday. 13 hrs. $50. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

February 21-23—**Electromyographic Interpretation.** UW at Olympic Hotel, Seattle. Thursday-Saturday. 16½ hrs. $126. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

February 23—**Venereal Disease.** UW. Saturday. 6½ hrs. $25. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

February 28-March 1—**Symposium on Respiratory Disease—12th Annual.** UW. Thursday-Friday. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

March 1—**Colposcopy.** UW. Friday. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

March 6-7—**Washington Circuit Course.** UW at Olympic Memorial Hospital, Port Angeles, and Everett General Hospital, Everett. Wednesday-Thursday. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash. Sch. of Med., E-350 HSB, SC-50, Seattle 98195. (206) 543-1050.

March 8-9—**Problem Solving in Gastroenterology.** Virginia Mason Medical Center. Friday-Saturday. 9 hrs. $35. Contact: Kenneth R. Wilske, MD, Dir., CME, Virginia Mason Med. Ctr., 111 Terry Ave., Seattle 98101. (206) 623-3700, ext. 470.

March 14-15—**Rehabilitation Medicine Course.** UW at University Towers Hotel, Seattle. Thursday-Friday. 13 hrs. $35. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

March 14-16—**Workshop in Clinical Neurology and Neurosurgery.** W/A RMP at Holiday Inn, Everett. Thursday-Friday. Contact: Neurological Associates, Pacific & Colby Building, 1515 Pacific, Everett 98201. (206) 259-0029.

March 14-16—**North Pacific Pediatric Society—Spring Meeting.** Washington Plaza Hotel, Seattle. Thursday-Saturday. Contact: C. Patrick Mahoney, MD, The Mason Clinic, 1118 9th Ave., Seattle 98101. (206) 623-3700.

March 15-17—**Radiology of the Skeletal System.** American College of Radiology at Seattle. Friday-Sunday. 15 hrs. $200.

for ACR members; $240 for non-members. Contact: ACR, 6900 Wisconsin Ave., Chevy Chase, Md. 20015.

March 16-17—**Sports Medicine Clinic—7th Annual.** W/A RMP at Sea-Tac Motor Inn, Seattle. Saturday-Sunday. 11 hrs. $50. Contact: Mr. Wayne Rasmussen, 5409 17th Ave., NW, Seattle 98107. (206) 782-3383.

March 22-23—**Dermatology: A Practical Approach to Common Problems.** Virginia Mason Medical Center. Friday-Saturday. 9 hrs. $50. Contact: Kenneth R. Wilske, MD, Dir., CME, Virginia Mason Med., Ctr., 111 Terry Ave., Seattle 98101. (206) 623-3700.

March 29—**Fetal Intensive Care.** UW at Child Development and Mental Retardation Center. Friday. 6½ hrs. $25. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

April 11-13—**Diagnostic Radiology.** Sacred Heart Medical Center, Spokane. Thursday-Saturday. 18 hrs. $60. Contact: Clyde A. Stevenson, MD, Sacred Heart Medical Center, Spokane 99204. (509) 455-3330.

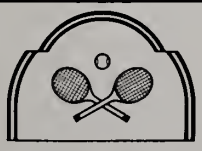
April 18-19. **Neurology and Psychiatry.** Thursday-Friday. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. School of Med. E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

April 19—**Tacoma Surgical Club—Annual Meeting.** Univ. of Puget Sound, Tacoma. Friday. Contact: Thomas J. Miskovsky, MD, 919 South 9th, Tacoma 98405. (206) MA 7-7143.

April 25-26—**Repiratory Care.** Health Sciences Thursday-Friday. 13 hrs. $75. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

April 26-27—**Clinical Cancer Conference.** Friday-Saturday. $50. Edgewater Inn. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

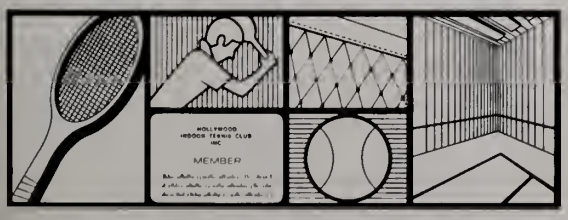
April 29-30. **Exercise Testing Workshop.** Monday-Tuesday. $80. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.



SOUTHERN CALIFORNIA'S FIRST and ONLY INDOOR TENNIS CLUB

NOW OPEN FOR PLAY

LIMITED MEMBERSHIPS NOW AVAILABLE



HOLLYWOOD INDOOR TENNIS CLUB, INC.

Now you can enjoy the climate-controlled convenience of playing tennis indoors year 'round...night and day ...with the finest playing conditions possible!

A membership in the Hollywood Indoor Tennis Club...which is private and limited...gives you tennis at its best. Court surfaces of Championship Laykold... perfect lighting and sound stage acoustics...showers, lockers, balcony viewing area, lounge and pro shop...all air filtered and temperature controlled.

For further information, you are invited to visit the club or call (213) 462-0727

HOLLYWOOD INDOOR TENNIS CLUB, INC.
1300 North Beachwood Drive at Fountain
Hollywood, California 90028

Index to The Western Journal of Medicine Advertising

Ayerst Laboratories
Premarin 4, 5

Bio-Science Laboratories
Laboratory Service 17

Books Received 28

Breon Laboratories, Inc.
Bronkotabs 12

Burroughs Wellcome Co.
Neosporin 27

Classified 24, 30

Compton Foundation 30

Flint Laboratories
Choloxin 31, 32
Synthroid 18, 19

Hollywood Indoor Tennis Club, Inc. 47

Howard Tours, Inc.
SFSU Travel Program 24

Eli Lilly Company
Kefzol 14, 15, 16
Keflex 26

Marion Laboratories, Inc.
Nico-400 ..... 36, 37

Mead Johnson Laboratories
Vasodilan 25

Medi-Fund Corp. 9

McNeil Laboratories
Parafon Forte 8, 9

Pharmaceutical Manufacturers Association
Prescription Ads 34, 35

Presto Foods Products, Inc.
Matey 3

The Purdue Frederick Company
Senokot (Geriatric) 7
Senokot (Cardiac) 13
Senokot (Traveller) 41

A. H. Robins Co.
Donnagel-PG/Robitussin 21, 22, 23

Reliable Mortgage Corporation 30

Roche Laboratories
Librium ..... 2nd Cover and Page 1

Sandoz Pharmaceuticals
Mellaril ..... Back Cover

G. D. Searle & Co.
Lomotil ..... 48 and Inside Back Cover

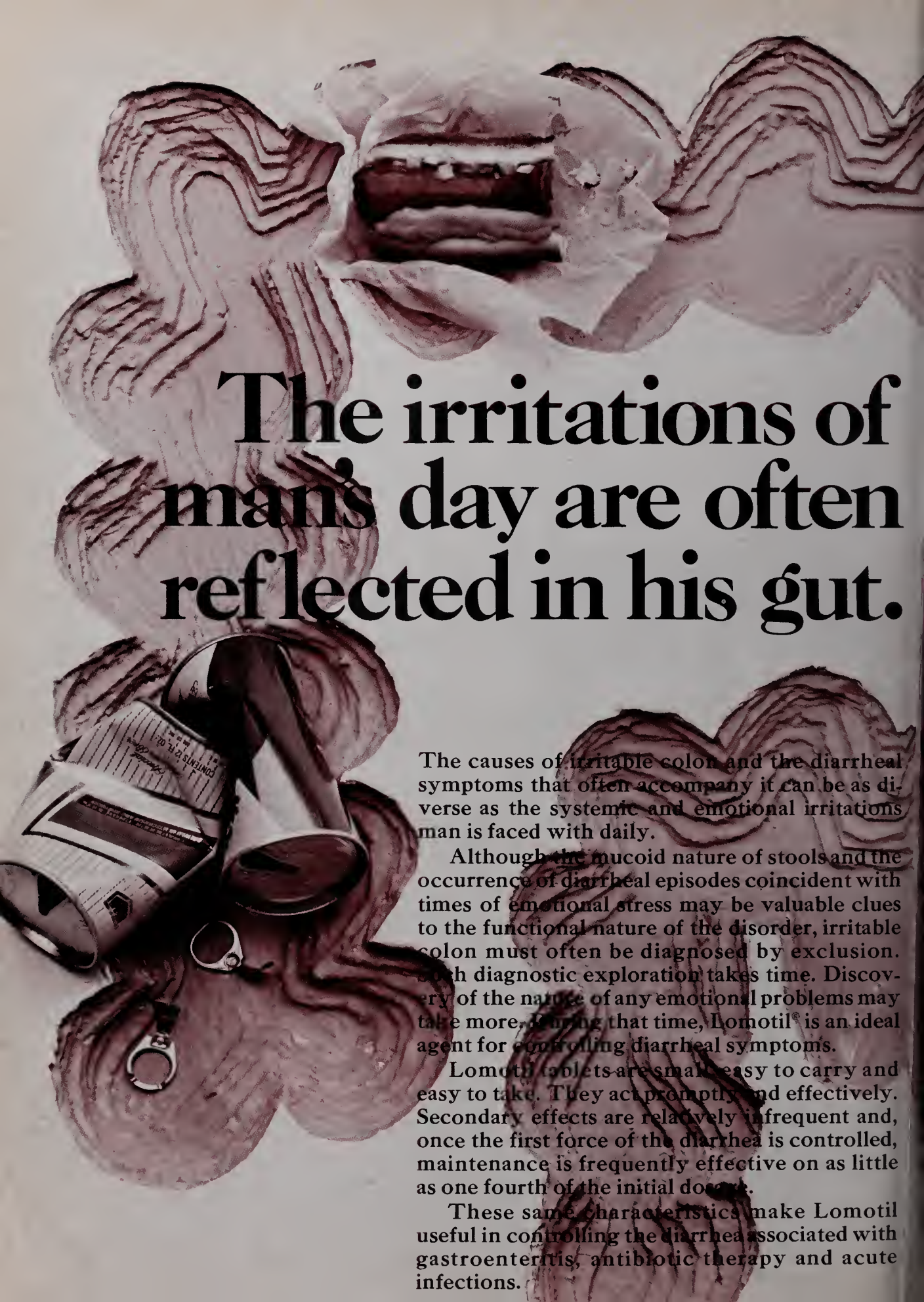
Smith Kline & French Laboratories
Ornade 45

Security Pacific National Bank 20

State Compensation Insurance Fund 6

Warner-Chilcott
Proloid 28, 29

Wyeth Laboratories
Bicillin/Wycillin 10, 11


The irritations of man's day are often reflected in his gut.
The causes of irritable colon and the diarrheal symptoms that often accompany it can be as diverse as the systemic and emotional irritations man is faced with daily.
Although the mucoid nature of stools and the occurrence of diarrheal episodes coincident with times of emotional stress may be valuable clues to the functional nature of the disorder, irritable colon must often be diagnosed by exclusion. Such diagnostic exploration takes time. Discovery of the nature of any emotional problems may take more. During that time, Lomotil® is an ideal agent for controlling diarrheal symptoms.
Lomotil tablets are small, easy to carry and easy to take. They act promptly and effectively. Secondary effects are relatively infrequent and, once the first force of the diarrhea is controlled, maintenance is frequently effective on as little as one fourth of the initial dosage.
These same characteristics make Lomotil useful in controlling the diarrhea associated with gastroenteritis, antibiotic therapy and acute infections.

Lomotil®

TABLETS/LIQUID

Each tablet and each 5 ml. of liquid contain:
diphenoxylate hydrochloride . . . 2.5 mg.
(Warning: May be habit forming)
atropine sulfate . . . . . 0.025 mg.

takes care of the gut issue in irritable colon

IMPORTANT INFORMATION: *This is a Schedule V substance by Federal law; diphenoxylate HCl is chemically related to meperidine. In case of overdosage or individual hypersensitivity, reactions similar to those after meperidine or morphine overdosage may occur; treatment is similar to that for meperidine or morphine intoxication (prolonged and careful monitoring). Respiratory depression may recur in spite of an initial response to Nalline® (nalorphine HCl) or may be evidenced as late as 30 hours after ingestion. LOMOTIL* IS NOT *AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN. THIS MEDICATION SHOULD BE KEPT OUT OF REACH OF CHILDREN.*

Indications: Lomotil is effective as adjunctive therapy in the management of diarrhea.

Contraindications: In children less than 2 years, due to the decreased safety margin in younger age groups, and in patients who are jaundiced or hypersensitive to diphenoxylate HCl or atropine.

Warnings: Use with caution in young children, because of variable response, and with extreme caution in patients with cirrhosis and other advanced hepatic disease or abnormal liver function tests, because of possible hepatic coma. Diphenoxylate HCl may potentiate the action of barbiturates, tranquilizers and alcohol. In theory, the concurrent use with monoamine oxidase inhibitors could precipitate hypertensive crisis.

Usage in pregnancy: Weigh the potential benefits against possible risks before using during pregnancy, lactation or in women of childbearing age. Diphenoxylate HCl and atropine are secreted in the breast milk of nursing mothers.

Precautions: Addiction (dependency) to diphenoxylate HCl is theoretically possible at high dosage. Do not exceed recommended dosages. Administer with caution to patients receiving addicting drugs or known to be addiction prone or having a history of drug abuse. The subtherapeutic amount of atropine is added to discourage deliberate overdosage; strictly observe contraindications, warnings and precautions for atropine; use with caution in children since signs of atropinism may occur even with the recommended dosage.

Adverse reactions: Atropine effects include dryness of skin and mucous membranes, flushing and urinary retention. Other side effects with Lomotil include nausea, sedation, vomiting, swelling of the gums, abdominal discomfort, respiratory depression, numbness of the extremities, headache, dizziness, depression, malaise, drowsiness, coma, lethargy, anorexia, restlessness, euphoria, pruritus, angioneurotic edema, giant urticaria and paralytic ileus.

Dosage and administration: ***Lomotil is contraindicated in children less than 2 years old.*** Use only Lomotil liquid for children 2 to 12 years old. For ages 2 to 5 years, 4 ml. (2 mg.) t.i.d.; 5 to 8 years, 4 ml. (2 mg.) q.i.d.; 8 to 12 years, 4 ml. (2 mg.) 5 times daily; adults, two tablets (5 mg.) t.i.d. to two tablets (5 mg.) q.i.d. or two regular teaspoonfuls (10 ml., 5 mg.) q.i.d. Maintenance dosage may be as low as one fourth of the initial dosage. Make downward dosage adjustment as soon as initial symptoms are controlled.

Overdosage: Keep the medication out of the reach of children since accidental overdosage may cause severe, even fatal, respiratory depression. Signs of overdosage include flushing, lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, tachycardia and respiratory depression which may occur 12 to 30 hours after overdose. Evacuate stomach by lavage, establish a patent airway and, when necessary, assist respiration mechanically. Use a narcotic antagonist in severe respiratory depression. Observation should extend over at least 48 hours.

Dosage forms: Tablets, 2.5 mg. of diphenoxylate HCl with 0.025 mg. of atropine sulfate. *Liquid,* 2.5 mg. of diphenoxylate HCl and 0.025 mg. of atropine sulfate per 5 ml. A plastic dropper calibrated in increments of ½ ml. (total capacity, 2 ml.) accompanies each 2-oz. bottle of Lomotil liquid.

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Address medical inquiries to:
G. D. Searle & Co., Medical Department
Box 5110, Chicago, Illinois 60680

MIXED ANXIETY-DEPRESSION* CUTS DEEP...

deep into the patient's family life

deep into the patient's ability to function in business

MELLARIL® (thioridazine)

TABLETS: 25 mg. thioridazine HCl, U. S. P.

A LOGICAL CHOICE FOR THE TREATMENT OF MODERATE TO SEVERE MIXED ANXIETY-DEPRESSION

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
Effective: The management of manifestations of psychotic disorders.
"Probably" effective: The relief of symptoms of neurotic depressive reaction; and control of moderate to severe agitation, hyperactivity, or aggressiveness in disturbed children.
"Possibly" effective: Alcohol withdrawal syndrome, intractable pain, psychoneuroses, senility.
Final classification of the less-than-effective indications requires further investigation.

Before prescribing or administering, see Sandoz literature for full product information. The following is a brief summary.

Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree.
Warnings: Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides. During pregnancy, administer only when the potential benefits exceed the possible risks to mother and fetus.
Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy may be avoided by remaining within the recommended limits of dosage. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving), and increase dosage gradually. Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension since phenothiazines may induce a reversed epinephrine effect on occasion. Daily doses in excess of 300 mg. should be used only in severe neuropsychiatric conditions.
Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—ECG changes (see *Cardiovascular Effects* below). *Other*—A single case described as parotid swelling.
The following reactions have occurred with phenothiazines and should be considered: *Autonomic Reactions*—Miosis, obstipation, anorexia, paralytic ileus. *Cutaneous Reactions*—Erythema, exfoliative dermatitis, contact dermatitis. *Blood Dyscrasias*—Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia. *Allergic Reactions*—Fever, laryngeal edema, angioneurotic edema, asthma. *Hepatotoxicity*—Jaundice biliary stasis. *Cardiovascular Effects*—Changes in terminal portion of electrocardiogram, including prolongation of Q-T interval, lowering and inversion of T-wave, and appearance of a wave tentatively identified as a bifid T or a U wave have been observed with phenothiazines, including Mellaril (thioridazine); these appear to be reversible and due to altered repolarization, not myocardial damage. While there is no evidence of a causal relationship between these changes and significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients showing characteristic electrocardiographic changes while taking the drug. While proposed, periodic electrocardiograms are not regarded as predictive. Hypotension, rarely resulting in cardiac arrest. *Extrapyramidal Symptoms*—Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonus, oculogyric crises, tremor, muscular rigidity, and akinesia. *Persistent Tardive Dyskinesia*—Persistent and sometimes irreversible tardive dyskinesia, characterized by rhythmical involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements) and sometimes of extremities may occur on long-term therapy or after discontinuation of therapy, the risk being greater in elderly patients on high-dose therapy, especially females; if symptoms appear, discontinue all antipsychotic agents. Syndrome may be masked if treatment is reinstituted, dosage is increased, or antipsychotic agent is switched. Fine vermicular movements of tongue may be an early sign, and syndrome may not develop if medication is stopped at that time. *Endocrine Disturbances*—Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema, false positive pregnancy tests. *Urinary Disturbances*—Retention, incontinence. *Others*—Hyperpyrexia; behavioral effects suggestive of a paradoxical reaction, including excitement, bizarre dreams, aggravation of psychoses, and toxic confusional states; following long-term treatment, a peculiar skin-eye syndrome marked by progressive pigmentation of skin or conjunctiva and/or accompanied by discoloration of exposed sclera and cornea; stellate or irregular opacities of anterior lens and cornea.

SANDOZ PHARMACEUTICALS, EAST HANOVER, N.J. 07936 73-751R SANDOZ

THE WESTERN Journal of Medicine

VOLUME 120 • NUMBER 3 **MARCH 1974**

183 *Coma, Hyperthermia and Bleeding Associated with Massive LSD Overdose—A Report of Eight Cases* JOHN C. KLOCK, MD, UDO BOERNER, MS, and CHARLES E. BECKER, MD

189 *Obstetrical Caudal Anesthesia in a Community Hospital—A Satisfactory Plan* LEON PARRISH FOX, MD, WILLIAM J. WELLER, MD, and HELEN WILDER, CRNA

193 *Lymphangiography—Its Practical Value in Surgically Staged Patients with Hodgkin's Disease* MICHAEL R. KADIN, MD, and RONALD W. THOMPSON, MD

200 *Human Infection with Vibrio Fetus* BRUCE FRANKLIN, MD, and DAVID D. ULMER, MD

MEDICAL PROGRESS

205 *The Role of Cellular Swelling in the Pathogenesis of Organ Ischemia* REX L. JAMISON, MD

SPECIALTY CONFERENCE

219 *Thromboembolism Diagnosis and Treatment*
Moderator: STANLEY L. SCHRIER, MD; Chief Discussant: ARTHUR J. SILVERGLEID, MD
From a House Staff Conference, Stanford University School of Medicine

MEDICAL STAFF CONFERENCE

226 *Hemophilia and von Willebrand's Disease—Fourth Annual Paul M. Aggeler Memorial Lecture*
Guest Lecturer: OSCAR D. RATNOFF, MD

233 IMPORTANT ADVANCES IN CLINICAL MEDICINE—*Ophthalmology*

237 EDITORIALS • *Are Carrots and Sticks for Donkeys, or for Doctors?* • *Death from Ischemia* • *Venous Thrombosis—Newer Diagnostic and Therapeutic Approaches* • *"Trauma Rounds"*

CASE REPORTS

241 *Eradication of Hepatitis B Antigen in Fulminant Hepatitis*
GARY L. GITNICK, MD, DAVID I. HANTMAN, MD, and SIDNEY C. MADDEN, MD

244 *Hemochromatosis Presenting as Diabetic Ketoacidosis with Extreme Hyperglycemia*
DERIK P. PASTERNAK, MD

247 *Psychogenic Pseudo-Sjögren's Syndrome*
J. DAVID BERNARD, MD, and MARTIN A. SHEARN, MD

249 LETTERS TO THE EDITOR

TRAUMA ROUNDS

252 *Penetrating Abdominal Wounds*
Chief Discussant: LYNN F. BAKER, MD; Editors: DONALD D. TRUNKEY, MD, and F. WILLIAM BLAISDELL, MD

MEDICAL SCHOOLS OF THE WEST

255 *University of Oregon Medical School*

GOVERNMENT AND MEDICINE

263 *Early and Periodic Screening—Medi-Screen Program Structure and Standard Setting*
JOHN J. McNAMARA, MD, MPH

NOTES FROM IMPORTANT OR UNUSUAL MEETINGS

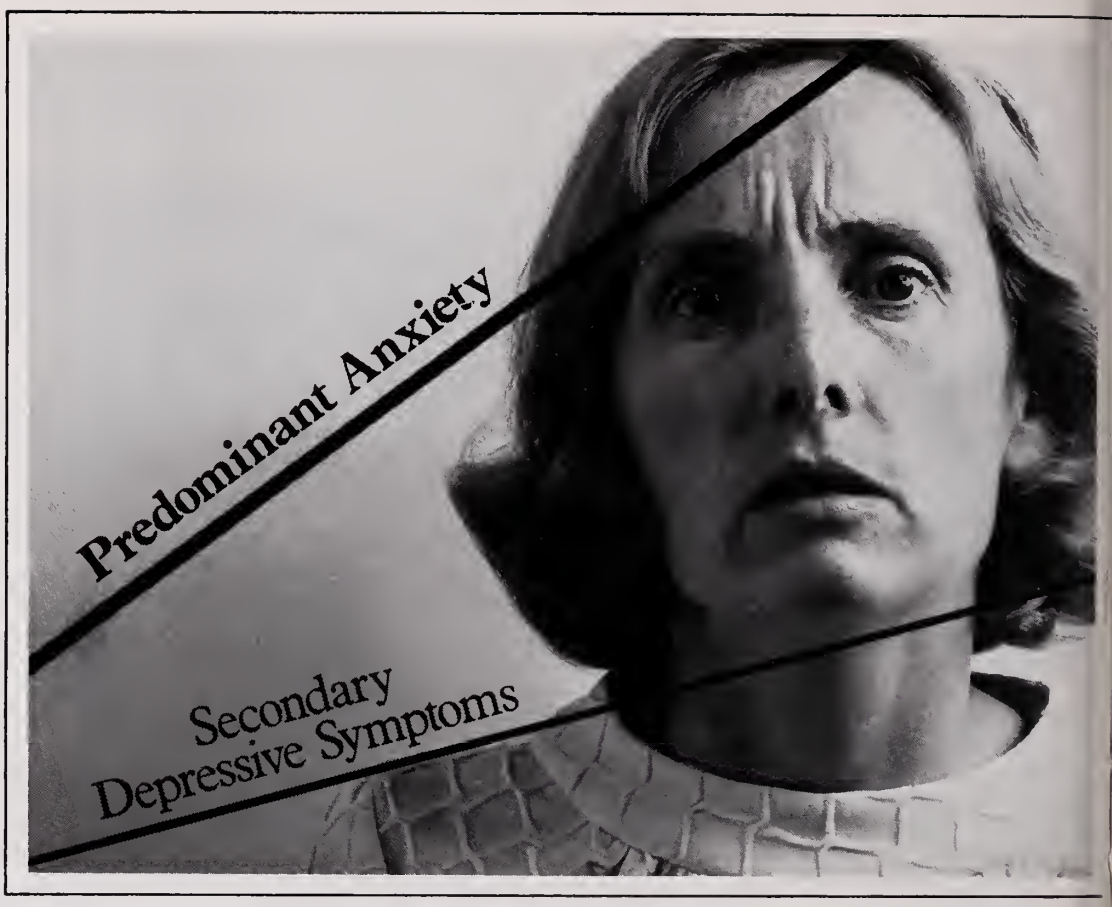
267 *Infection Control in the Hospital—A Report on Workshop Discussions* DAVID A. STEVENS, MD

270 *Book Reviews*

271 *In Memoriam*

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII; OREGON; WASHINGTON, MONTANA, AND ALASKA**
(See Advertising Page 40)

01%-EXC 022874 SUB050020010
NEW ENG JRL MED
10 SHATTUCK
BOSTON
MA 02115



This psychoneurotic often responds

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal ma be associated with temporary increase in frequency and/or severit of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdraw symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiti and sweating). Keep addiction-pro individuals under careful surveillance because of their predisposit to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

When you determine that the depressive symptoms are associated with or secondary to predominant anxiety in the psychoneurotic patient, consider Valium (diazepam) in addition to reassurance and counseling, for the psychotherapeutic support it provides. As anxiety is relieved, the depressive symptoms referable to it are also often relieved or reduced.

The beneficial effect of Valium is usually pronounced and rapid. Improvement generally becomes evident within a few days, although some patients may require a longer period. Moreover, Valium (diazepam) is generally well tolerated. Side effects most commonly reported are drowsiness, ataxia and fatigue. Caution your patients against engaging in hazardous occupations or driving.

Frequently, the patient's symptoms are greatly intensified at bedtime. In such situations, Valium offers an additional advantage: adding an *h.s.* dose to the *b.i.d.* or *t.i.d.* schedule can relieve the anxiety and thus may encourage a more restful night's sleep.

ymptom complex o Valium® (diazepam)

Precautions: If combined with er psychotropics or anticonvul- ts, consider carefully pharma- ogy of agents employed; drugs h as phenothiazines, narcotics, biturates, MAO inhibitors and er antidepressants may poten- e its action. Usual precautions icated in patients severely de- ssed, or with latent depression, with suicidal tendencies. Observe al precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

OCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

Valium® 2-mg, 5-mg, 10-mg tablets
(diazepam)

At Your Service in The Golden State

In the region named *California* by Spanish adventurers probably after the name of a treasure island in a popular Spanish tale . . .

PHARMACEUTICAL DIVISION
MARION
LABORATORIES, INC.
KANSAS CITY, MISSOURI 64137

is represented by . . .

Dick Bastin

Vito Bell

Mel Bergman

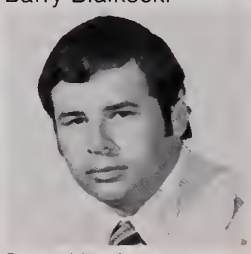
Barry Bialkoski

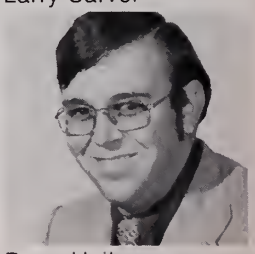
Larry Carver

Dave Evans

Bob Fatch

Richard Foss

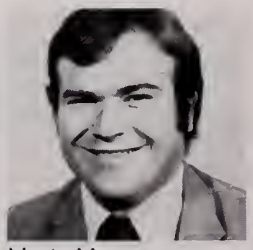

Dave Hawks

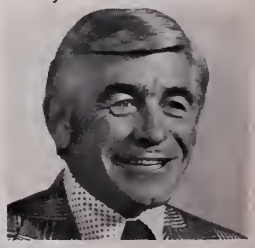

Barry Heilman

Bob Jones

Randy Kennick

Ruth MacKie

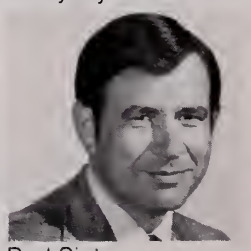

Marty Myers


Bill Palmer

John Patella

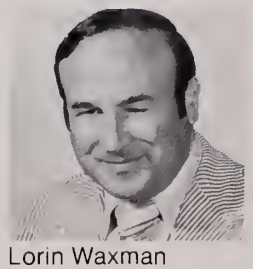
Jim Petric

Mike Ryan


Bud Sinkey

Ernie Smith

Bill Stauch


Lorin Waxman

Frank Yannarell

These representatives bring you . . . . . .

Puts comfort in your prescription for nicotinic acid

escription: Each capsule contains 400 mg of
icotinic acid in a special base that provides
rolonged systemic effect
dications: NICO-400® is recommended for all
sease states in which nicotinic acid has
en used. These include conditions
sociated with deficient circulation and for
e in the correction of nicotinic acid
c encies.
ntraindications: Individuals with a
persensitivity to nicotinic acid, severe
ypotension or hemorrhaging.
rnings: Use with caution in those patients
h history of peptic ulcer, severe diabetes,
pa red gall bladder or liver functions and
pregnant women.
verse Reactions: Patients should be
rmed of the short-lived reactions
per enced with nicotinic acid therapy:
eous flushing, a sensation of warmth,
ng and itching of the skin, increased
trointestinal motility and sebaceous
d activity.
age and Administration: One capsule
ry 12 hours or as directed by physician.
ion: Federal law prohibits dispensing
hout prescription.
w Supplied: Bottles of 100 capsules.

other patient benefit product from
PHARMACEUTICAL DIVISION
MARION LABORATORIES INC
KANSAS CITY, MISSOURI 641

THE OPTIMAL DOSE, 400-mg, timed-release NICO-400® (nicotinic acid) capsule provides

- Controlled flushing for the desired effects without therapy-limiting side effects.
- Convenient b.i.d. dosage that's less likely to be forgotten.
- The economy of nicotinic acid medication.

For comfort wherever nicotinic acid is used

NICO-400®

(nicotinic acid) Plateau CAPS®

THE WESTERN Journal of Medicine

Since 1902 • Formerly California Medicine

OWNED AND PUBLISHED BY THE CALIFORNIA MEDICAL ASSOCIATION
731 MARKET ST. • SAN FRANCISCO, CA 94103 • TELEPHONE (415) 777-2000

editorial communications to:
MALCOLM S. M. WATTS, M.D., *Editor*

business communications to:
LYTTON O. HETLAND, *Business Manager*

. . .

LLOYD H. SMITH, JR., M.D., *Associate Editor*
ROBERT F. EDWARDS, *Managing Editor*
DAVID GREER, *Associate Managing Editor*

Editorial Board

Chairman of the Board
Malcolm S. M. Watts, San Francisco

Allergy
Norman Shure, Los Angeles
Abba I. Terr, San Francisco

Anesthesiology
Ronald L. Katz, Los Angeles

Dermatology
George F. Odland, Seattle
Rees B. Rees, San Francisco
Richard B. Stoughton, La Jolla

General and Family Practice
Robert L. Hippen, San Diego
Herbert A. Holden, San Leandro

General Surgery
Frederick M. Anderson, Reno
Richard E. Gardner, San Francisco
Lucius D. Hill, Seattle

Industrial Medicine and Toxicology
Thomas H. Milby, Berkeley

Internal Medicine
Robert J. Bolt, Davis
J. David Bristow, Portland
Marcus A. Krupp, Palo Alto
Robert G. Petersdorf, Seattle
Donald W. Petit, Los Angeles
Edgar Wayburn, San Francisco
Nathan J. Zvaifler, San Diego

Neurology
Pierre M. Dreyfus, Davis
Robert A. Fishman, San Francisco
Phillip D. Swanson, Seattle

Obstetrics and Gynecology
Ralph C. Benson, Portland
William J. Dignam, Los Angeles
Ernest W. Page, San Francisco

Ophthalmology
David O. Harrington, San Francisco
Robert S. Hepler, Los Angeles

Orthopedics
Rodney K. Beals, Portland
John A. Blosser, Oakland
Paul E. McMaster, Beverly Hills

Otolaryngology
Mansfield F. W. Smith, San Jose
Paul H. Ward, Los Angeles

Pathology
Richard L. Kempson, Stanford
Averill A. Liebow, San Diego

Pediatrics
Robert E. Greenberg, Los Angeles
William L. Nyhan, San Diego
Henry R. Shinefield, San Francisco
Paul F. Wehrle, Los Angeles

Pharmacology
Sydney M. Finegold, Los Angeles
Kenneth L. Melmon, San Francisco

Physical Medicine and Rehabilitation
Elizabeth S. Austin, Los Angeles
Glenn G. Reynolds, San Jose

Plastic Surgery
Richard L. Dakin, San Rafael
N. John Wilde, Fresno

Psychiatry
Carl Eisdorfer, Seattle
Leon J. Epstein, San Francisco
George L. Mallory, Los Angeles
Helen Tausend, Los Angeles

Public Health
J. M. Stubblebine, Sacramento
Irma M. West, Sacramento

Radiology
H. Joachim Burhenne, San Francisco
Robert B. Engle, Pasadena
Melvin M. Figley, Seattle

Thoracic and Cardiac Surgery
John E. Connolly, Irvine
Albert Starr, Portland

Urology
Thomas F. Conroy, San Mateo
Ruben F. Gittes, La Jolla

Consultants in Medical Services and Health Care
Gerald A. Besson, Sunnyvale
Paul Scholten, San Francisco

Policy Committee—Editorial Board

THOMAS N. ELMENDORF ..... Willows
STANLEY A. MOORE ..... San Diego
JOSEPH F. BOYLE ..... Los Angeles
HENRY V. EASTMAN ..... Tustin
E. KASH ROSE ..... Napa
HELEN B. WEYRAUCH ..... San Francisco
MALCOLM S. M. WATTS ..... San Francisco

Advertisements—THE WESTERN JOURNAL OF MEDICINE is published the first week of each month. Advertising copy must be received not later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee.

SALES REPRESENTATIVES: JOHN H. HARLING, INC.

EAST:
SAUL HORNIK
655 AMBOY AVENUE
WOODBRIDGE, N.J. 07095
TEL. (201) 636-7150

MIDWEST:
JOHN HARLING • JAMES ANTON
18 SO. MICHIGAN AVE.
CHICAGO, ILL. 60603
TEL. (312) 641-0755

WEST:
MELVIN B. TYLER
731 MARKET ST.
SAN FRANCISCO, CA. 94103
TEL. (415) 777-2000

Copyright, 1974, by the California Medical Association.

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the non-commercial purpose of scientific or educational advancement.

Subscription prices, $8 ($9 for foreign countries); student subscription $4; single copies 80 cents.

Volumes begin with the first of January and the first of July. Subscriptions may commence at any time.

Change of Address—Requests for change of address should give both the old and new address.

CONTRIBUTIONS OF SCIENTIFIC AND ORIGINAL ARTICLES

Responsibilities for Statements and Conclusions in Original Articles—Authors are responsible for all statements, conclusions and methods of presenting their subjects. These may or may not be in harmony with the views of the editorial staff. It is aimed to permit authors to have as wide latitude as the general policy of the Journal and the demands on its space may permit. The right to reduce, revise or reject any manuscript is always reserved.

Exclusive Publication—Articles are accepted for publication on condition that they are contributed solely to this Journal. Ordinarily contributors will be notified within 60 days if a manuscript is accepted for publication. Every effort will be made to return unused manuscripts.

Length of Articles—Ordinarily articles should not exceed 3,000 words (approximately 5 printed pages). Under exceptional circumstances only will articles of over 4,000 words be published.

Manuscripts—Manuscripts should be typewritten, double spaced and the original typescript plus one copy submitted.

Illustrations—Ordinarily publication of 2 or 3 illustrations accompanying an article will be paid for by THE WESTERN JOURNAL OF MEDICINE. Any number beyond this might have to be paid for by the author.

References—Should conform to the following order: name of author, title of article, name of periodical, with volume, inclusive pages, month and year—i.e.: Lee GS: The heart rhythm following therapy with digitalis—In theory and practice. Arch Int Med 44:554-562, Dec 1942. They should be listed in the order in which they are cited in the text, numbered in sequence and punctuated as above.

Reprints—Reprints must be paid for by the author at established standard rates.

CONTRIBUTIONS OF "LETTERS TO THE EDITOR"

The Editorial Board will be glad to receive and consider for publication letters containing information of general interest to physicians or presenting constructive criticisms on issues of the day.

"Entered as second class matter at the post office in San Francisco and additional mailing offices under the Act of March 3, 1879." Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized August 10, 1918.

situation:

Chronic disease... requires constant medication... often several different drugs...

constipation:

A number of drugs may interfere with the regular bowel action... antacids, anticholinergics, narcotics, antispasmodics, barbiturates, antihypertensives, antidepressants, tranquilizers... and many others...

laxation:

SENOKOT Tablets or Granules effectively counteract drug-induced constipation... do not interfere with primary medication ...act gently and predictably.

Supplied: SENOKOT Tablets (small, easy-to-swallow)—Bottles of 50 and 100. SENOKOT Granules (delicious, cocoa-flavored)—4 ,8 and 16 ounce (1 lb.) canisters.

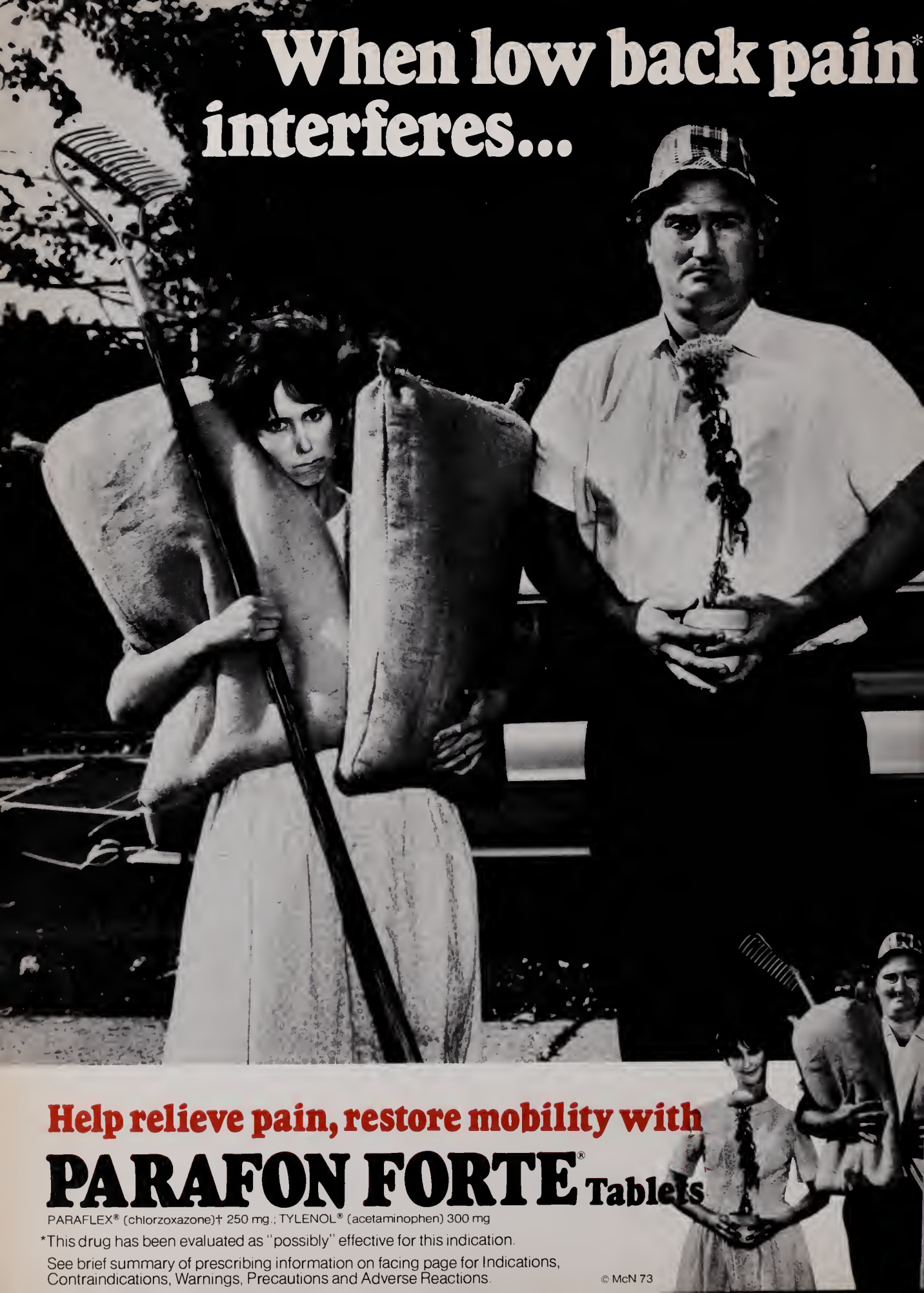
SENOKOT Tablets Granules

(standardized senna concentrate)

a natural laxative

PURDUE FREDERICK

© COPYRIGHT 1974, THE PURDUE FREDERICK COMPANY
NORWALK, CONN. 06856 A7286 136974


When low back pain*
interferes...
Help relieve pain, restore mobility with
PARAFON FORTE® Tablets
PARAFLEX® (chlorzoxazone)† 250 mg.; TYLENOL® (acetaminophen) 300 mg
*This drug has been evaluated as "possibly" effective for this indication.
See brief summary of prescribing information on facing page for Indications, Contraindications, Warnings, Precautions and Adverse Reactions.
© McN 73

PARAFON FORTE® Tablets help relieve pain, restore mobility and stop pain-spasm feedback by providing:

a nonsalicylate analgesic equal to aspirin for relief of pain,[1,2] yet unlikely to cause the gastric irritation,[2,3] allergic reactions[2] or increased bleeding time[4] associated with aspirin therapy.

and a skeletal muscle relaxant shown in extensive clinical studies to be useful in a variety of low back disorders[5-7]* but which is not an antihistamine or tranquilizer derivative and is unlikely to produce a tranquilizing or sedative effect.[8]

***Indications** Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective for the relief of severe skeletal muscle pain and spasm when associated with acute disorders of the lower back (including acute exacerbations of chronic conditions).

Contraindications: Sensitivity to either component.
Warnings: *Usage in Pregnancy*—Use in woman of child-bearing potential only when potential benefits outweigh possible risks.
Precautions: Exercise caution in patients with known allergies or history of drug allergies. If a sensitivity reaction or any signs or symptoms suggestive of liver dysfunction are observed, the drug should be stopped.
Adverse Reactions: Occasionally, drowsiness, dizziness, lightheadedness, malaise, overstimulation or gastrointestinal disturbances may be noted; rarely, allergic-type skin rashes, petechiae, ecchymoses, angioneurotic edema or anaphylactic reactions. In rare instances, *Paraflex* (chlorzoxazone) may possibly have been associated with gastrointestinal bleeding. While *Paraflex* (chlorzoxazone) and chlorzoxazone-containing products have been suspected as being the cause of hepatic toxicity in approximately eighteen patients, it was not possible to state that the dysfunction was or was not drug induced.
Usual Adult Dosage: Two tablets q.i.d.
Supplied: Scored, light green tablets, imprinted "McNEIL"—bottles of 100.

References: 1. Batterman, R.C., and Grossman, A.J. Fed. Proc. *14* 316, 1955. 2. Goodman, L.S., and Gilman, A., ed.: The Pharmacological Basis of Therapeutics, ed. 4. New York, The Macmillan Company, 1970. 3. Vickers, F.N. Gastroint. Endosc. *14* 94, 1967. 4. Mielke, C.H., Jr., and Britten, A.F.H. New Engl. J. Med. *282* 1270, 1970 (Corresp.). 5. Vernon, W.G. Curr. Therap. Res. *14* 801, 1972. 6. Scheiner, J.J. Curr. Therap. Res. *14* 168, 1972. 7. Walker, J.M. Curr. Therap. Res. *15* 248, 1973. 8. Friend, D.G. Clin. Pharmacol. Ther. *5* 871, 1964.

†U.S. Patent No. 2,895,877

McNEIL — McNeil Laboratories, Inc. Fort Washington, Pa. 19034

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

THE ABORTION EXPERIENCE—Psychological & Medical Impact—Howard J. Osofsky, MD, Professor, Department of Obstetrics and Gynecology, Temple University Hospital Health Sciences Center, Philadelphia; and Joy D. Osofsky, PhD, Associate Professor, Department of Psychology, Temple University, Philadelphia. Medical Department, Harper & Row, Publishers, Inc., 2350 Virginia Avenue, Hagerstown, MD (21740), 1973. 688 pages, $25.00.

ACUPUNCTURE: A SELECTED BIBLIOGRAPHY—Volume 1: 1800-1972—David E. Bresler, PhD, Director of Research, and Patricia L. Wisne, AB, Research Associate, National Acupuncture Association. National Acupuncture Association, 1033 Gayley Avenue, Los Angeles (90024), 1973. 129 pages, $10.00 (Students and Member: $7.50).

ADVANCES IN CARDIOVASCULAR SURGERY (Clinical Cardiology Monographs—Series Consultants, J. Willis Hurst, MD, and Dean T. Mason, MD)—Edited by John W. Kirklin, MD, Charles and Fay Kerner Professor of Surgery and Chairman of the Department of Surgery, School of Medicine and Medical Center, University of Alabama in Birmingham, Birmingham. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 279 pages, $15.75.

ALCOHOL AND YOUR HEALTH—Louise Bailey Burgess. Charles Publishing Company, Inc., 8350 Santa Monica Boulevard, Los Angeles (90069), 1973. 243 pages, $12.50.

ALLERGY MANAGEMENT IN CLINICAL PRACTICE—Louis Tuft, MD, Clinical Professor of Medicine (Emeritus) and formerly Chief of the Allergy Clinic, Temple University Medical Center, Philadelphia. The C. V. Mosby Company, 3301 Washington Boulevard, St. Louis, MO (63103), 1973. 426 pages, $29.75.

THE ANESTHESIOLOGIST, MOTHER AND NEWBORN—Edited by Sol M. Shnider, MD, Professor of Anesthesia, Obstetrics & Gynecology, Director of Obstetrical Anesthesia, University of California, San Francisco; and Frank Moya, MD, Professor and Chairman, Department of Anesthesiology, University of Miami Medical School. The Williams & Wilkins Company, 428 East Preston, Baltimore (21202), 1974. 295 pages, $16.50.

ATLAS OF VASCULAR SURGERY—Third Edition—Falls B. Hershey, MD, FACS, Associate Professor of Clinical Surgery, Washington University School of Medicine, St. Louis, MO.; Chief of Vascular Surgery, St. John'e Mercy Medical Center; formerly Director, St. Louis Heart Association Artery Bank; formerly Chairman, Department of Surgery, Michael Reese Hospital and Medical Center, Chicago, Ill.; Diplomate, American Board of Surgery and Carl H. Calman, MD, FACS, formerly Assistent in Clinicel Surgery, Washington University School of Medicine, St. Louis, MO.; Diplomate, American Board of Surgery. The C. V. Mosby Company, 3301 Washington Boulevard, St. Louis, MO (63103), 1973. 504 pages, $35.00.

BLEEDING PROBLEMS—Diagnosis & Treatment—Joseph A. Caprini, MD, Assistant Professor of Surgery, Northwestern University Medicel School, Assistant Attending Physician, Evanston Hospital, Evanston, Illinois. Medical Department, Harper & Row, Publishers, 2350 Virignia Avenue, Hagerstown, MD (21740), 1973. 63 pages, $2.95.

CHILDHOOD LEARNING, BEHAVIOR, AND THE FAMILY—Louise C. Taichert, MD. Behavioral Publications, 2852 Broadway, New York City (10025), 1973. 112 pages, $7.95.

CLINICAL RESEARCH FOR ALL—Cyril Maxwell, MB, ChB, Medicel Director and Director of Studies, Clinical Research Services Limited, London; Foreword by Professor W. Linford Rees, MD, FRCP, FRC Psych, DPM, Professor of Psychiatry, University of London. Cambridge Medical Publications Limited, 435/437 Wellingborough Road, Northempton NN1 4EZ, England, 1973. 165 pages, $8.00.

COMMENTS IN SPORTS MEDICINE—Edited by Timothy T. Creig, PhD. The American Medical Association, Order Handling Department, 535 N. Dearborn Street, Chicago (60610), 1973. 230 pages, $5.00 (Paperbeck).

CURRENT MEDICAL DIAGNOSIS & TREATMENT—Marcus A. Krupp, MD, Clinical Professor of Medicine, Stanford University School of Medicine (Stanford); Director of Research, Palo Alto Medical Research Foundation; Director of Laboratories, Palo Alto Medical Clinic; and Milton J. Chatton, MD, Clinical Associate Professor of Medicine, Stanford University School of Medicine (Stanford); Senior Attending Physician, Sante Clere Valley Medicel Center (San Jose); Research Associate, Palo Alto Medical Research Foundation (Palo Alto); and associete euthors; Lenge Medicel Publications, Drawer L, Los Altos, CA (94022), 1974. 1,018 pages, $12.00 (Paperback).

CURRENT PEDIATRIC THERAPY—6—Sydney S. Gellis, MD, Professor and Chairmen, Depertment of Pediatrics, Tufts University School of Medicine, Pediatrician-in-Chief, Boston Floating Hospital for Infents and Children, Tufts-New England Medicel Center, Boston; and Benjemin M. Kegan, MD, Director, Department of Pediatrics, Cedars of Lebenon Hospitel, Division of Cedars-Sinal Medical Center; Professor of Pediatrics, University of Celifornia at Los Angeles. W. B. Seunders Compeny, West Washington Square, Philedelphie (19105), 1973. 870 pages, $26.50.

(Continued on Page 38)

FROM SYNTEX...
A unique approach in the adjunctive management of severe perennial bronchial asthma

20 mg CAPSULES

[CROMOLYN SODIUM]

aarane®

may decrease the severity of clinical symptoms of asthma, or the need for concomitant therapy, or both.

aarane is *different*. It is neither a bronchodilator, nor an antihistamine, nor an anti-inflammatory. The *aarane* mechanism of action is *prophylactic*. Because of this, *aarane* has no role in the treatment of an acute attack of asthma.

In vitro and *in vivo* animal studies have shown that *aarane* interferes with the chain of events *before* the release of chemical mediators of the asthma process. *aarane appears to inhibit the release of these mediators.*

Prophylactic in mechanism of action—significantly different in its delivery system—*aarane* may decrease the severity of clinical symptoms of asthma, or the need for concomitant therapy, or both.

E CAUSE THIS DRUG AND ITS DELIVERY SYSTEM ARE UNIQUE, THE PHYSICIAN IS ENCOURAGED TO
3TAIN ADDITIONAL INFORMATION FROM HIS LOCAL SYNTEX REPRESENTATIVE.
SEE LAST PAGE FOR BRIEF SUMMARY.

SYNTEX

aarane® 20 mg CAPSULES

[CROMOLYN SODIUM]

DOSAGE IS ONE *aarane* CAPSULE FOUR TIMES DAILY.

INDICATIONS

aarane (cromolyn sodium) is indicated as an adjunct in the management of patients with severe perennial bronchial asthma. Such patients must have a significant bronchodilator-reversible component to their airway obstruction as demonstrated by a generally accepted pulmonary function test of airway mechanics. *aarane* has no role in the treatment of an acute attack of asthma, especially status asthmaticus.

If improvement occurs, it will ordinarily occur within the first two-to-four weeks of administration, as manifested by a decrease in the severity of clinical symptoms of asthma, or in the need for concomitant therapy, or both.

A decision to continue the administration of *aarane* on a long term basis is justified if introduction of the drug into the patient's regimen:

- produces a significant reduction in the severity of the clinical symptoms of asthma, or
- permits a significant reduction in or elimination of steroids, or
- permits better management of patients who have intolerable side effects to sympathomimetic agents or methylxanthines.

CONTRAINDICATIONS

aarane is contraindicated in those patients who have shown hypersensitivity to it.

WARNINGS

***aarane* HAS NO ROLE IN THE TREATMENT OF AN ACUTE ATTACK OF ASTHMA, ESPECIALLY STATUS ASTHMATICUS.**

In some animal toxicity studies, a previously unreported proliferative arterial lesion found predominantly in the kidneys occurred in both treated and untreated macaque monkeys. The possibility that the increased incidence of the lesion in the treated monkeys is due to the administration of cromolyn sodium can neither be affirmed nor refuted. (For additional details, see Animal Toxicology in the package insert.) The relevance of these data to man is unknown. In considering the long term administration of cromolyn sodium to a patient, the physician should take into consideration the possible risk as well as the degree of efficacy achieved in the individual patient.

In view of the biliary and renal routes of excretion for *aarane*, (cromolyn sodium), consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Eosinophilic pneumonia has been reported rarely in association with the administration of cromolyn sodium. If this occurs the drug should be discontinued.

Use in pregnancy: Reproduction studies have been performed in rabbits, rats and mice. Adverse fetal effects (increased resorptions, decreased fetal weight) were noticed only at very high parenteral doses that produced maternal toxicity. The relevance to the human is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established and its use in pregnancy is not recommended.

Use in children: Clinical experience in children under 5 years of age is limited due to the necessity for administration by inhalation. Use of *aarane* is not recommended for such children. Because of the possibility that adverse effects of the drug could become apparent only after many years, a benefit-risk consideration of the long term use of *aarane* is particularly important in pediatric patients.

Unique carrying case holds *aarane*® Inhaler and one day's dosage of four individually foil-wrapped capsules.

PRECAUTIONS

Occasionally patients may experience cough and/or bronchospasm following *aarane* inhalation. At times, patients with *aarane* induced bronchospasm may not be able to continue its administration despite prior bronchodilator administration.

Symptoms of asthma may recur if *aarane* is reduced below the recommended dosage, or discontinued.

ADVERSE REACTIONS

Instances of maculopapular rash and urticaria, which have been reported, have cleared promptly upon withdrawing the drug. Occasionally patients may experience cough and/or bronchospasm following *aarane* inhalation.

HOW SUPPLIED

aarane® (cromolyn sodium) capsules, each containing 20 mg cromolyn sodium in strips of four capsules each, in trade packages of 60 capsules. *aarane* Inhalers are supplied separately in individual containers.

Caution: Federal law prohibits dispensing without prescription.

SYNTEX

SYNTEX LABORATORIES, INC.
PALO ALTO, CALIFORNIA 94304

Sign of a cold* sufferer

Time for Ornade®

Each Spansule® capsule contains 8 mg. Teldrin® (brand of chlorpheniramine maleate); 50 mg. phenylpropanolamine hydrochloride; 2.5 mg. isopropamide, as the iodide.

Fast relief of nasal congestion and hypersecretion* with convenient b.i.d. dosage.

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Possibly effective: For relief of upper respiratory tract congestion and hypersecretion associated with vasomotor rhinitis and allergic rhinitis, and for prolonged relief.

Lacking in substantial evidence of effectiveness: For relief of nasal congestion and hypersecretion associated with the common cold and sinusitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Hypersensitivity to any component; concurrent MAO inhibitor therapy; severe hypertension; bronchial asthma; coronary artery disease; stenosing peptic ulcer; pyloroduodenal or bladder neck obstruction. Children under 6.

Warnings: Caution patients about activities requiring alertness (e.g., operating vehicles or machinery). Warn patients of possible additive effects with alcohol and other CNS depressants.

Usage in Pregnancy: In pregnancy, nursing mothers and women who might bear children, weigh potential benefits against hazards. Inhibition of lactation may occur.

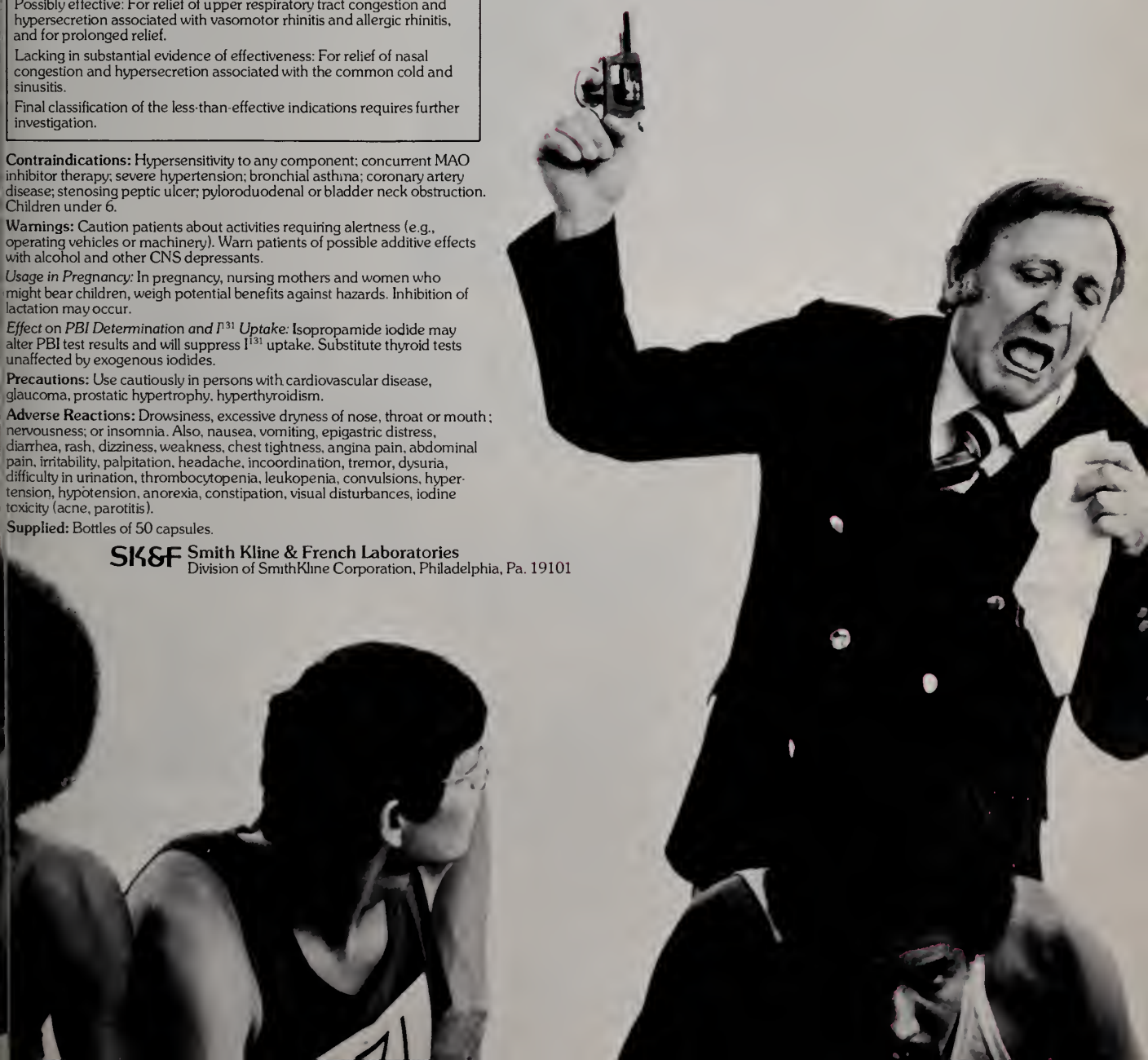
Effect on PBI Determination and I^{131} Uptake: Isopropamide iodide may alter PBI test results and will suppress I^{131} uptake. Substitute thyroid tests unaffected by exogenous iodides.

Precautions: Use cautiously in persons with cardiovascular disease, glaucoma, prostatic hypertrophy, hyperthyroidism.

Adverse Reactions: Drowsiness, excessive dryness of nose, throat or mouth; nervousness; or insomnia. Also, nausea, vomiting, epigastric distress, diarrhea, rash, dizziness, weakness, chest tightness, angina pain, abdominal pain, irritability, palpitation, headache, incoordination, tremor, dysuria, difficulty in urination, thrombocytopenia, leukopenia, convulsions, hypertension, hypotension, anorexia, constipation, visual disturbances, iodine toxicity (acne, parotitis).

Supplied: Bottles of 50 capsules.

SK&F Smith Kline & French Laboratories
Division of SmithKline Corporation, Philadelphia, Pa. 19101



Tofranil-PM®

imipramine pamoate

Capsules* of 75 mg. and 150 mg.

Provides the therapeutic effectiveness of divided daily doses with no loss of safety.

*Each capsule contains imipramine pamoate equivalent to 75 mg. or 150 mg. of imipramine hydrochloride.

ne dose lasts from bedtime to bedtime.

: single-dose therapy in depression
en the dosage is established.

acilitates optimal daily dosage with
ne 150-mg. capsule—for many pa-
ents the dosage needed for optimal
elief.

nay markedly reduce the probability
f missed doses.

ffers dosage convenience that as-
ures greater patient cooperation.

ecomes part of the regular bedtime
outine—making it easier to establish
more reliable pattern of self-med-
cation.

- offers the therapeutic equivalency of divided daily doses of Tofranil®, imipramine hydrochloride, with no loss of efficacy or safety.
- has the convenience and flexibility of single daily dosage strengths.
- saves time and cost of dosage administration in the hospital.

Please read the prescribing information for details of usage, precautions, warnings, contraindications, adverse experiences, and dosage recommendations. A summary of this information appears on the following page.

Tofranil-PM® Geigy
imipramine pamoate

Capsules* of 75 mg. and 150 mg.

*Each capsule contains imipramine pamoate equivalent to 75 mg. or 150 mg. of imipramine hydrochloride.

One dose lasts from bedtime to bedtime.

Tofranil-PM®
brand of imipramine pamoate
Tofranil®
brand of imipramine hydrochloride USP

Indications: For the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than other depressive states.
Contraindications: The concomitant use of monoamine oxidase inhibiting compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur in patients receiving such combinations. The potentiation of adverse effects can be serious, or even fatal. When it is desired to substitute Tofranil, brand of imipramine hydrochloride, in patients receiving a monoamine oxidase inhibitor, as long an interval should elapse as the clinical situation will allow, with a minimum of 14 days. Initial dosage should be low and increases should be gradual and cautiously prescribed The drug is contraindicated during the acute recovery period after a myocardial infarction. Patients with a known hypersensitivity to this compound should not be given the drug The possibility of cross-sensitivity to other dibenzazepine compounds should be kept in mind
Warnings: *Usage in Pregnancy:* Safe use of imipramine during pregnancy and lactation has not been established; therefore, in administering the drug to pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards. Animal reproduction studies have yielded inconclusive results. There have been clinical reports of congenital malformation associated with the use of this drug, but a causal relationship has not been confirmed.
Extreme caution should be used when this drug is given to:
- patients with cardiovascular disease because of the possibility of conduction defects, arrhythmias, myocardial infarction, strokes and tachycardia;
- patients with increased intraocular pressure, history of urinary retention, or history of narrow-angle glaucoma because of the drug's anticholinergic properties;
- hyperthyroid patients or those on thyroid medication because of the possibility of cardiovascular toxicity;
- patients with a history of seizure disorder because this drug has been shown to lower the seizure threshold;
- patients receiving guanethidine or similar agents since imipramine may block the pharmacologic effects of these drugs.

Usage in Children: Pending evaluation of results from clinical trials in children, Tofranil, brand of imipramine hydrochloride, is not recommended for treatment of depression in patients under twelve years of age.
Tofranil-PM, brand of imipramine pamoate, should not be used in children of any age because of the increased potential for acute overdosage due to the high unit potency (75 mg and 150 mg.). Each capsule contains imipramine pamoate equivalent to 75 mg or 150 mg. imipramine hydrochloride.
Since imipramine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as operating an automobile or machinery, the patient should be cautioned accordingly.

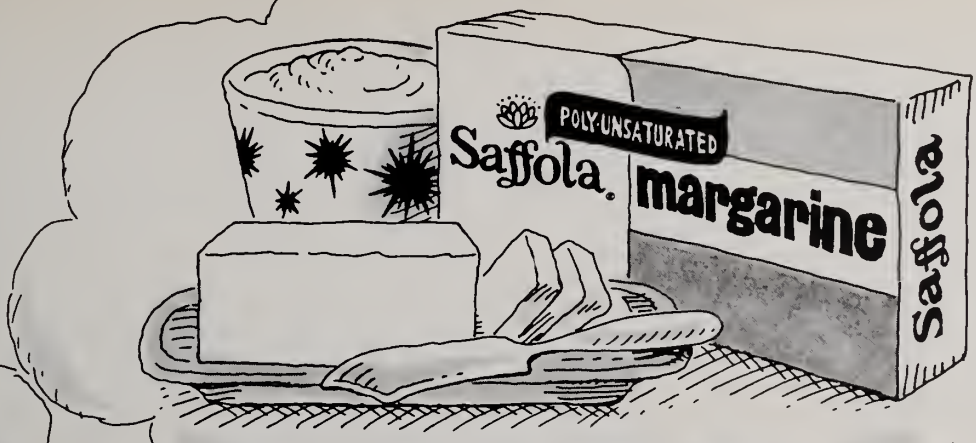
Precautions: It should be kept in mind that the possibility of suicide in seriously depressed patients is inherent in the illness and may persist until significant remission occurs. Such patients should be carefully supervised during the early phase of treatment with Tofranil, brand of imipramine hydrochloride, and may require hospitalization. Prescriptions should be written for the smallest amount feasible.
Hypomanic or manic episodes may occur, particularly in patients with cyclic disorders. Such reactions may necessitate discontinuation of the drug If needed, Tofranil, brand of imipramine hydrochloride, may be resumed in lower dosage when these episodes are relieved Administration of a tranquilizer may be useful in controlling such episodes.
Prior to elective surgery, imipramine hydrochloride should be discontinued for as long as the clinical situation will allow.
An activation of the psychosis may occasionally be observed in schizophrenic patients and may require reduction of dosage and the addition of a phenothiazine.
In occasional susceptible patients or in those receiving anticholinergic drugs (including antiparkinsonism agents) in addition, the atropine-like effects may become more pronounced (e.g., paralytic ileus). Close supervision and careful adjustment of dosage is required when this drug is administered concomitantly with anticholinergic or sympathomimetic drugs.
Avoid the use of preparations, such as decongestants and local anesthetics, which contain any sympathomimetic amine (e.g., adrenalin, noradrenalin), since it has been reported that tricyclic antidepressants can potentiate the effects of catecholamines.
Patients should be warned that the concomitant use of alcoholic beverages may be associated with exaggerated effects.
Both elevation and lowering of blood sugar levels have been reported
Concurrent administration of imipramine with electroshock therapy may increase the hazards; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.
Adverse Reactions: Note: Although the listing which follows includes a few adverse reactions which have not been reported with this specific drug, the pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when imipramine is administered.
Cardiovascular: Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke, falls
Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis
Neurological: Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alterations in EEG patterns; tinnitus.
Anticholinergic: Dry mouth, and, rarely, associated sublingual adenitis; blurred vision, disturbances of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

Allergic: Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue); drug fever; cross-sensitivity with desipramine.
Hematologic: Bone marrow depression including agranulocytosis; eosinophilia; purpura; thrombocytopenia Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathological neutrophil depression.
Gastrointestinal: Nausea and vomiting, anorexia, epigastric distress, diarrhea; peculiar taste, stomatitis, abdominal cramps, black tongue.
Endocrine: Gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels.
Other: Jaundice (simulating obstructive); altered liver function; weight gain or loss; perspiration; flushing; urinary frequency; drowsiness, dizziness, weakness and fatigue; headache; parotid swelling; alopecia.
Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache and malaise.
Dosage and Administration: Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients as compared to hospitalized patients who will be under close supervision. Dosage should be initiated with Tofranil, brand of imipramine hydrochloride, at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a longer period of time, at the lowest dose that will maintain remission.
Once-a-day maintenance dosage can be provided with Tofranil-PM, brand of imipramine pamoate, capsules if this dosage has been established as explained above. This dose may be given at bedtime. For the occasional patient who manifests stimulation and insomnia with this dosage regimen, the capsules may be given in the morning.
Parenteral administration should be used only for starting therapy in patients unable or unwilling to use oral medication. The oral form should supplant the injectable as soon as possible.
How Supplied: Tofranil, brand of imipramine hydrochloride: Round tablets of 25 and 50 mg.; triangular tablets of 10 mg.; and ampuls, each containing 25 mg. in 2 cc. for I.M. administration.
Tofranil-PM, brand of imipramine pamoate: Capsules of 75 and 150 mg (Each capsule contains imipramine pamoate equivalent to 75 or 150 mg of imipramine hydrochloride.)
(B) 98-146-850-O (12/73)

For complete details, including dosage and administration, please refer to the full prescribing information.

GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

TO 9848



Safflower oil margarine helps reduce blood cholesterol.*

Doctor's view:

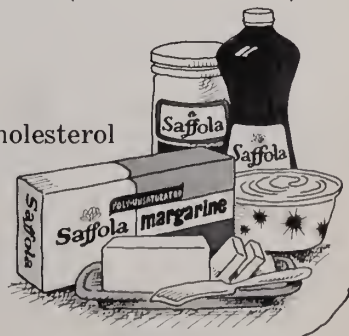
From where you sit, it's important that safflower oil is 30% higher in poly-unsaturates than corn oil. That means that margarine, cooking oil, and mayonnaise are higher in poly-unsaturates when made from safflower oil than when made from corn oil.

Saffola® margarine tastes like butter.

Patient's view:

From where he sits, a low saturated fat diet is easier to follow because Saffola tastes as good as butter or any premium margarine (corn oil included).

Usually there are two sides to a low cholesterol diet—the clinical side and the human side. Happily, in the case of Saffola, you and your patients don't have to take sides.



Saffola

*in conjunction with a low saturated fat diet

Must vasodilators and therapy for other diseases come into conflict?

not if the vasodilator is

VASODILAN®
(ISOXSUPRINE HCl)

the compatible vasodilator... no treatment conflicts reported

The cerebral or peripheral vascular disease patient often has coexisting disease[1] which calls for another drug along with his vasodilator. It may be a hypoglycemic, miotic, antihypertensive, diuretic, anticoagulant, corticosteroid, or coronary vasodilator.

Vasodilan is not incompatible with any of these drugs—no treatment conflict has been reported. And, unlike other vasodilators, Vasodilan has not been reported to affect carbohydrate metabolism, liver function, or intraocular pressure—or to complicate treatment of diabetes, hypertension, peptic ulcer, glaucoma, or liver disease.

In fact, there are no known contraindications to the use of Vasodilan in recommended oral doses, other than that it should not be given in the presence of frank arterial bleeding or immediately postpartum.

1. Gertler, M. M., et al.: Geriatrics *25*:134-148 (May) 1970.

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.
3. Threatened abortion.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.

Dosage and Administration: 10 to 20 mg. three or four times daily.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Adverse Reactions: On rare occasions, oral administration of the drug has been associated in time with the occurrence of severe rash. When rash appears, the drug should be discontinued. Occasional overdosage effects such as transient palpitation or dizziness are usually controlled by reducing the dose.

Supplied: Tablets, 10 mg.—bottles of 100, 1000, 5000 and Unit Dose; 20 mg.—bottles of 100, 500 and Unit Dose.

© 1973 MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA 47721 U.S.A. 734017

Mead Johnson LABORATORIES

When you see anxiety-look for depression
NORPRAMIN®
(desipramine hydrochloride)

when depression is primary

NORPRAMIN®
(desipramine hydrochloride)

HELPS PROVIDE EARLY CONTROL OF DEPRESSIVE SYMPTOMS...

Anxiety is an invidious symptom. It feeds upon sickness, gnaws, grows and invades every cranny of psychic pathology adding intensity to torment. Anxiety as a symptom secondary to depression may be so dominant that it obscures the primary diagnosis. It may suggest treatment with tranquilizers which often help. But as the vampire of legend had to have a laurel stake driven through its heart to truly die, so anxiety secondary to depression will not cease to nibble and bite until an antidepressant eradicates the primary illness—and symptomatic anxiety starves.

IN BRIEF:

Indications: Norpramin® (desipramine hydrochloride) is indicated for the relief of depressive symptoms. Endogenous depressions are more likely to be alleviated than others.

Contraindications: Desipramine hydrochloride should not be given within two weeks of treatment with a monoamine oxidase inhibitor. Contraindications include the acute recovery period following myocardial infarction and hypersensitivity to the drug. Cross sensitivity with other dibenzazepines is a possibility.

Warnings: 1. Extreme caution should be used in patients: (a) with cardiovascular disease, (b) with a history of urinary retention or glaucoma, (c) with thyroid disease or those on thyroid medication, (d) with a history of seizure disorder. 2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds. 3. *Use in Pregnancy:* Safe use during pregnancy and lactation has not been established. 4. *Use in Children:* Norpramin® (desipramine hydrochloride) is not recommended for use in children. 5. This drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Therefore, the patient should be cautioned accordingly.

Precautions: This drug should be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with drugs of this class. If possible, dispense in child-resistant containers. It shoufd be kept out of reach of children. Reduce dosage, or alter treatment, if serious adverse effects occur. Norpramin® (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates and may cause exacerbation of phychosis in schizophrenic patients. Use cautiously with anticholinergic or sympathomimetic drugs. Response to alcoholic beverages may be exaggerated. In the concurrent administration of ECT and antidepressant drugs one should consider the possibility of increased risk relative to benefits. Discontinue as soon as possible prior to elective surgery because of possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients on desipramine hydrochloride. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is neutropenia.

Adverse Reactions: *Cardiovascular:* hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. *Psychiatric:* confusional states (especially in the elderly), hallucinations, disorientation, delusions; anxiety, agitation; insomnia and nightmares; hypomania; exacerbation of phychosis. *Neurological:* paresthesias of extremities; incoordination, ataxia, tremors, peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus. *Anticholinergic:* dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, hypotonic bladder. *Allergic:* skin rash, petechiae, urticaria, itching, photosensitization, edema (of face and tongue or general), drug fever. *Hematologic:* agranulocytosis, eosinophilia, purpura, thrombocytopenia. *Gastrointestinal:* anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue. *Endocrine:* gynecomastia, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, testicular swelling; elevation or depression of blood sugar levels. *Other:* jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia. *Withdrawal Symptoms:* Though not indicative of addiction, abrupt cessation after prolonged therapy may produce nausea, headache and malaise.

Dosage and Administration: *The usual adult dose:* 50 mg. three times daily; increase if necessary after 7 to 10 days to maximum of 200 mg. daily. Dosage above 200 mg. per day are not recommended. *Maintenance:* At a lower dose adequate to maintain remission. *Adolescent and geriatric patient dose:* 25 to 100 mg. daily if necessary.

Overdosage: There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug. The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous prassure and regulation of fluid- and acid-basa balance are well known in most medical centers. If heart failure is imminent, digitalize promptly.

Manufactured by LAKESIDE LABORATORIES
Division of Colgate Palmolive Company

Distributed by
LAKESIDE LABORATORIES, I
Milwaukee, Wisconsin 53201

Bank of America gives fast relief from financial upset three ways:

1. Professional Term Loans. Suffering from lack of funds to update your equipment, remodel or expand your quarters—or just want some extra working capital on-hand? Our financing is designed to meet your special needs, promptly and painlessly, and with flexible terms. (For those just starting practice, financing based on projected income is also available.) And your Bank of America Loan Officer can assist you with lease-hold improvements, too.

2. Professional Billing and BankAmericard® Services. Give your business a shot in the arm with one of the most sophisticated financial control systems available. Our customized services streamline bookkeeping, can boost efficiency and profits, and help all aspects of your practice run more smoothly. At a cost that's easy to swallow.

3. Personal Trust Services. Expert management of stocks and bonds, real estate, property and tax matters is your prescription for financial security and peace of mind. Our Trust Officer will work out a plan tailor-made to the individual needs of your family.

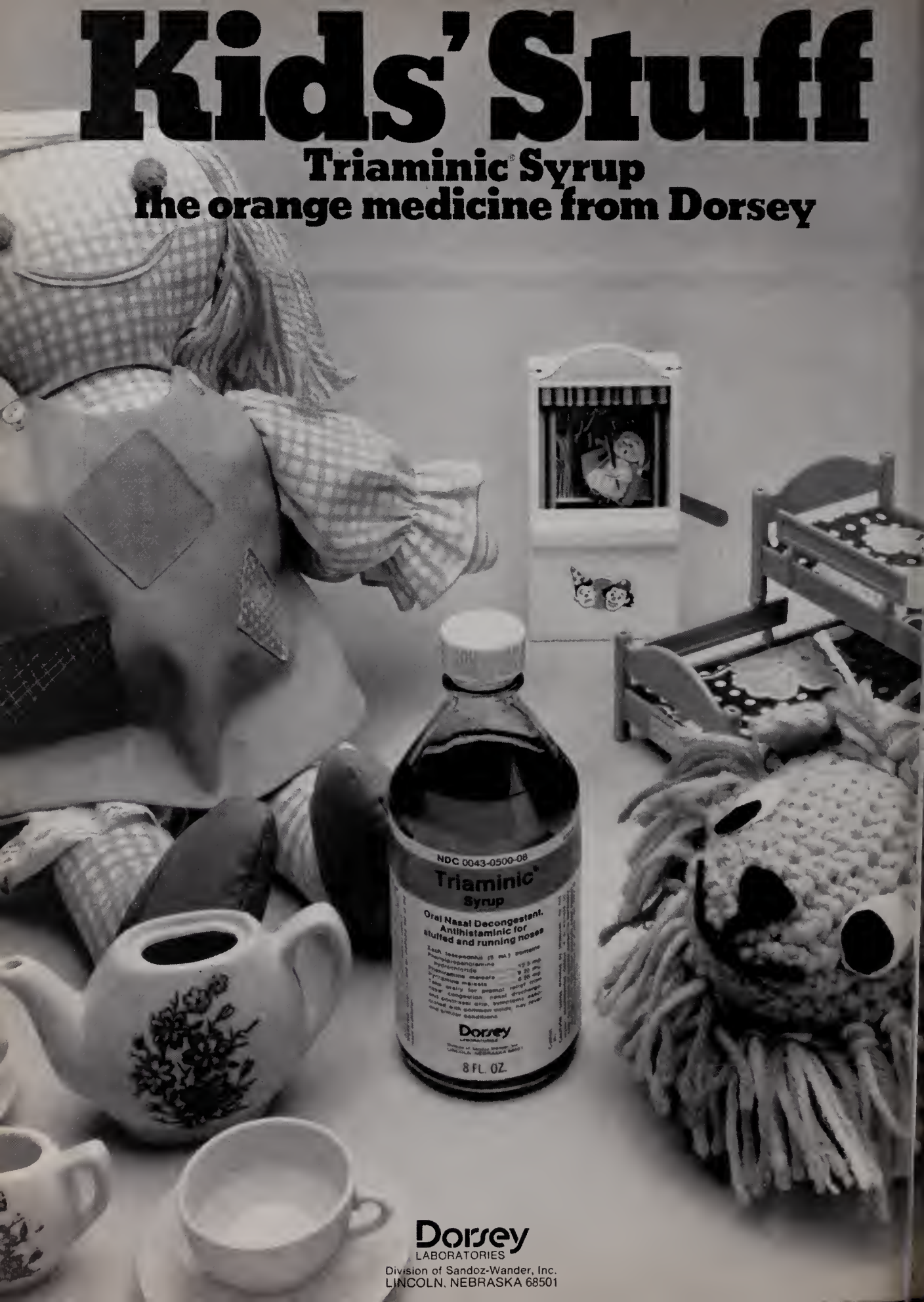
With over two decades of administering to the financing needs of medical professionals, you could call us the "Money Specialists." (No other bank can offer you this much experience.) Shouldn't you make an appointment for your financial check-up with Bank of America today? You'll feel a lot better tomorrow.

BANK OF AMERICA

BANK OF AMERICA N.T.&S.A. • MEMBER FDIC

Kids' Stuff

Triaminic® Syrup
the orange medicine from Dorsey



Dorsey
LABORATORIES
Division of Sandoz-Wander, Inc.
LINCOLN, NEBRASKA 68501

Our prescription for your practice: Take MediManager and get plenty of sleep.

Security Pacific Bank is glad to introduce MediManager: A comprehensive financial management package for the physician and dentist.

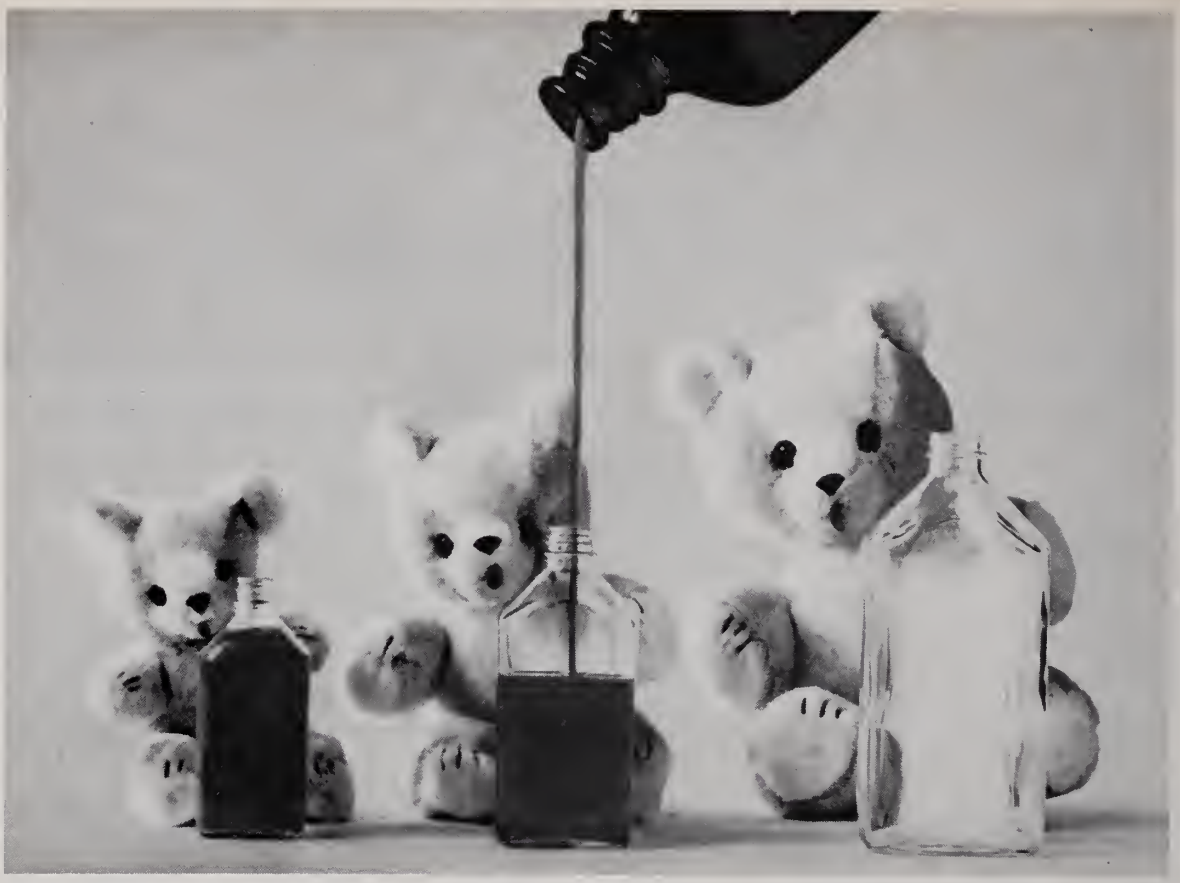
MediManager is the most complete professional service package ever offered to physicians and dentists. It's designed to be of help in (1) patient billing and collection, (2) patient credit, (3) equipment financing, (4) acquisition of facilities, and (5) estate management.

MediManager features a computerized patient billing service with insurance form preparation capabilities. It offers remittance banking and payroll help, as well as a unique patient credit plan that gives you prompt payment for your services. MediManager provides commercial and real estate loans, equipment loans and leasing, auto leasing and locational assistance. Finally, it can help you with trusts, pension plans and profit-sharing programs.

Ask your branch manager about MediManager: Something special from Security Pacific Bank.

SECURITY PACIFIC BANK
SOMETHING SPECIAL

© 1973 SECURITY PACIFIC NATIONAL BANK MEMBER FDIC



Not too little, not too much... but just right!

"Just right" amounts of Ilosone Liquid 250 can be dispensed easily from the pint bottle in *any* quantity you specify to meet your patients' precise needs—without regard to package size.

ready-mixed

ILOSONE® LIQUID 250

ERYTHROMYCIN ESTOLATE

(equivalent to 250 mg. erythromycin per 5-ml. teaspoonful)

Additional information available to the profession on request.

DISTA

Dista Products Company
Division of Eli Lilly and Company
Indianapolis, Indiana 46206

400054

THE WESTERN
Journal of Medicine

Refer to: Klock JC, Boerner U, Becker CE: Coma, hyperthermia and bleeding associated with massive LSD overdose—A report of eight cases. West J Med 120:183-188, Mar 1973

Eight patients were seen within 15 minutes of intranasal self-administration of large amounts of pure D-lysergic acid diethylamide (LSD) tartrate powder. Emesis and collapse occurred along with signs of sympathetic overactivity, hyperthermia, coma and respiratory arrest. Mild generalized bleeding occurred in several patients and evidence of platelet dysfunction was present in all. Serum and gastric concentrations of LSD tartrate ranged from 2.1 to 26 nanograms per ml and 1,000 to 7,000 μg per 100 ml, respectively. With supportive care, all patients recovered. Massive LSD overdose in man is life-threatening and produces striking and distinctive manifestations.

Coma, Hyperthermia and Bleeding Associated with Massive LSD Overdose

A Report of Eight Cases

JOHN C. KLOCK, MD
UDO BOERNER, MS
CHARLES E. BECKER, MD
San Francisco

ALTHOUGH THERE HAVE BEEN many reports of overdose with D-lysergic acid diethylamide (LSD) in man, little toxicologic data are available. The physiologic effects of LSD in doses greater than 1 mg have not been studied in man and the lethal dose must be interpolated from animal studies. We performed extensive toxicologic studies on eight people who took large doses of LSD; the results and clinical-toxicologic correlations are reported herein.

From the Division of Clinical Pharmacology, the Toxicology Laboratory, and the Medical Service, San Francisco General Hospital, and the Department of Medicine, University of California, San Francisco.

Presented by invitation at the American Academy of Clinical Toxicology Meeting, San Diego, California, August 2, 1973.

Submitted August 30, 1973.

Reprint requests to: J. C. Klock, MD, Department of Medicine, Division of Hematology, Room 506 M, University of California, San Francisco, San Francisco, CA 94143.

Reports of Cases

On 29 July 1972, four women and four men ranging in age from 19 to 39 years were admitted to the emergency room at San Francisco General Hospital for drug overdose. Following a dinner party, they had "snorted" (inhaled through a straw placed in one nostril) a small amount of cocaine and a quantity of white powder believed to be cocaine. All eight were reported to have snorted at least two "lines" (rows of powder measuring approximately 3 × 4 × 30 mm) of the second substance. Within 5 minutes they experienced anxiety, restlessness, generalized parasthesias and muscle discomfort, vomiting and physical collapse. Ten minutes later they were admitted to the emergency room in varying degrees of intoxication (Table 1 and Appendix).

TABLE 1.—*Clinical Manifestations of Massive LSD Overdose in Eight Patients*

Patient No.	*Age, Sex*	*Blood Pressure (mm Hg)*	*Respirations (breaths/min)*	*Pulse (beats/min)*	*Temperature (°F)*	*Pupils (mm)*	*Bleeding*	*Other*
1	20 ♀	130/90	6	120	104.0	8	+	Coma, respiratory arrest
2	19 ♀	130/30	33	200	107.0	7	+	Coma, respiratory arrest, diarrhea
3	28 ♀	160/60	24	150	99.5	8	−	Writhing and dystonic movements, diarrhea
4	33 ♀	110/70	9	110	98.0	8	+	Coma, respiratory arrest, aspiration
5	39 ♂	130/80	20	120	100.8	7	−	Coma, aspiration
6	29 ♂	230/130	30	112	98.8	6	−	Coma, aspiration
7	28 ♂	130/80	20	170	98.6	6	−	Hyperactive, psychotic, hallucinating
8	28 ♂	190/95	20	120	102.4	7	+	Hyperactive, psychotic, hallucinating

Figure 1.—Gross appearance of the blood clot from Patient 1 and a normal control clot (left) and results of autologous serum incubation at 37°C for 6 hours of clots from Patient 1 and a normal control clot (right). The normal control specimen is to the right in each picture.

Five were comatose when first seen and most were extremely hyperactive with severe visual and auditory hallucinations at some point during their course. Three required endotracheal intubation and assisted ventilation and three aspirated vomitus. All had sinus tachycardia, widely dilated and fixed pupils, emesis, flushing and sweating. Fever developed in four and diarrhea in two. Transient hypertension was present in three patients and no patient had convulsions. All had coagulopathy as manifested by the inability to form firm clots and absence of clot retraction in the blood specimen tubes. Seven had guaiac-positive vomitus and four showed exidence of mild generalized bleeding (microscopic hematuria in two, gross hematuria in two, oozing at venipuncture sites in three and small amounts of blood in the vomitus or stool in all four patients).

Laboratory data showed normal or negative values (see Appendix) for the following: blood glucose and serum sodium, potassium, and bicarbonate levels, hemoglobin (13.0 to 16.4 grams per deciliter), platelet count (186,000 to 458,000 per microliter), prothrombin time (11.0 to 12.5 seconds) and partial thromboplastin time (19.3 to 38.7 seconds), chest roentgenograms and electrocardiograms. Results of liver and renal function tests were within normal limits in the three patients studied. Direct examination of the blood clots and results of clot retraction tests on several patients showed friable clots that fell apart easily without dissection, and absence of clot retraction (Figure 1). Supportive care included respiratory assistance, use of hypothermic blankets, and administration of antibiotics and corticosteroids when indicated. Bleeding was mild and disappeared within 4 to 6 hours. Blood transfusions were unnecessary and all patients recovered completely within 12 hours. All were discharged or left the hospital within 48 hours of admission. No residua were observed in a year of direct follow-up of five patients.

Toxicologic Data

Specimens of blood, urine and gastric contents were obtained on admission from seven patients and analyses were performed as follows.

Gastric Content

Extraction of the gastric contents for toxicologic screening was performed according to the method of Sunshine[1] and analyzed by thin layer

TABLE 2.—*Toxicologic Data Obtained in Seven Patients with Massive LSD Overdose**

Patient No.	Blood: Ethanol (%)	Blood: Cocaine† (μg/ml)	Blood: LSD (ng/ml)	Urine Cocaine† (μg/ml)	Gastric LSD (mg/100 ml)
1 ...	0	0	NT	0	7.0
2 ...	0.08	0	NT	1.3	NT
3 ...	0	0	26.0	10.0	NT
4 ...	NT	NT	NT	NT	1.2
5 ...	0	0	6.6	0	<1 mg
6 ...	4	0	11.6	0	NT
7 ...	0.02	0	2.1	NT	3.1

*NT=not tested.
†Measured as benzoylecgonine.

chromatography according to a modified method of Mulé.[2] All basic gastric content extracts showed the presence of an ergot alkaloid. By the photodegradation method of Andersen[3] and using a combination of eight reference substances,* this substance was further characterized as D-lysergic acid diethylamide. The results, shown in Table 2, were confirmed by mass spectrography.† The mass peaks of the isolated material corresponded with those reported in the literature and those of authenticated LSD-25, which was used as a control sample.

Urine

Preliminary screening by Mulé's[2] method of thin layer chromatography showed possible traces of cocaine in some specimens. Therefore, specimens were rechecked by homogeneous enzyme immunoassay[4] for benzoylecgonine, the main cocaine metabolite in urine.[5] Two of the urine specimens contained small amounts of benzoylecgonine (Table 2).

Blood

Blood was analyzed for LSD by the back extraction method of Aghajanian and Bing[6] and the results were compared with standards of serum containing 5, 10, 20 and 40 nanograms (ng) LSD per ml. All specimens analyzed contained LSD (Table 2). Blood was analyzed for cocaine, using the same general method as for urine, and for ethanol and other volatile substances, using gas chromatography.[7] No specimen contained cocaine and two specimens contained small amounts of ethanol (Table 2).

Confiscated Material

A white flaky material (208 mg) was confiscated by police and identified as the large quantity of powder used at the party. Analysis by thin layer chromatography, fluorescent analysis, mass spectrography and the melting point and mix melting point identified this substance as almost pure (80 to 90 percent) D-lysergic acid diethylamide tartrate.

Discussion

Intranasal administration of crushed LSD tablets is a common method of administration by LSD users when a rapid onset of action is desired. The active use of this route by our patients was corroborated by the onset of symptoms soon after administration of the white powder, the absence of LSD in screening samples of food and wine from the party and the absence of symptoms in members of the party who did not use the powder. The lethal dose of LSD for man is not known, but it ranges from 46 mg per kg in mice[8] to 0.3 mg per kg in rabbits[8] to 0.1 mg per kg in Asiatic elephants.[9] Interpolated for the body weight of man, this would result in a lethal dose of 0.2 mg per kg or an approximate lethal dose of 14,000 μg.[8] The toxicologic data and the purity of the powder used by our patients indicate that milligram amounts of the drug were administered, placing the patients at risk of having severe and possibly lethal reactions.

LSD is capable of many and varied physiologic, psychologic and biochemical effects.[8,10,11] Most of these effects are thought to be due to LSD's ability to affect 5-hydroxytryptamine receptors both centrally and peripherally[12-14] and to its generalized stimulation of the reticulocortical system.[8] The previously observed physiologic manifestations of psychosis, hyperexcitability, tachycardia, mydriasis[8,15,16] and hyperthermia[17] were prominent in our patients, but the degree of central nervous system depression and respiratory inhibition that occurred in these patients has only been demonstrated in animals given very large doses.[8] Furthermore, the generalized bleeding problem observed in four of our patients has not been described before with LSD. The clinical and laboratory data suggest that platelet function was abnormal. Little literature on LSD and platelet function is available. However, Michal[18] showed that LSD-25 in 1

*D-lysergic acid diethylamide tartrate (LSD-25®, Sandoz), ergotamine tartrate (Sandoz), methysergid(e) maleate (Sansert®, Sandoz), methylergonovine maleate (Methergine®, Sandoz), ergonovine maleate (Ergotrate® maleate, Lilly), dihydroergotamine (methanesulfonate) (DHE-45®, Sandoz), D-lysergamide tartrate (ergine), D-iso-lysergamide tartrate (iso-ergine tartrate).

†Varian NAT-GNOME quadropol mass spectrograph, Varian Associates, Palo Alto, California.

to 3 nanomolar concentrations could significantly inhibit 5-hydroxytryptamine-induced platelet aggregation *in vitro;* no effect on adenosine diphosphate-induced aggregation was noted. Cocaine also affects platelet function *in vitro* in much larger concentration.[19,20] Our analytical data do not indicate that cocaine played a significant role in these cases, making the possibility of cocaine-induced platelet dysfunction unlikely. However, more evidence is needed before LSD can be implicated as the cause of the bleeding in these patients.

Treatment of our patients was entirely supportive and recovery was relatively rapid. Some of them were able to converse after 4 to 5 hours and all were normal within 12 hours. Most did not remember being brought to the hospital; otherwise, no apparent psychologic or physical ill effects were noted in a year of follow-up examinations of five patients. Most of the patients continue to use LSD intermittently. Death from LSD overdose still has not been confirmed toxicologically; nevertheless, the rapid administration of large doses of LSD in man is associated with striking and distinctive clinical manifestations and is life-threatening.

APPENDIX

PATIENT 1. A 20-year-old woman was comatose and unresponsive to pain with vomitus in the mouth and hypopharynx on arrival at San Francisco General Hospital. Breathing was shallow, irregular and ineffective; the pupils were dilated and unreactive. There were hyperactive bowel sounds, but no diarrhea. Bleeding at venipuncture sites persisted for more than 20 minutes. The hemoglobin was 13.9 grams per deciliter (dL), packed cell volume 43.2 percent, platelets 245,000 per microliter (μL), and white blood cell count 19,000 per μL with 35 percent segmented neutrophils, 2 percent eosinophils, 1 percent basophils, and 62 percent lymphocytes. On urinalysis there was a 2 plus reaction for blood. The blood urea nitrogen was 9 mg and creatinine 0.7 mg per dL, serum sodium was 140 mEq, potassium 4.4 mEq, chloride 108 mEq and bicarbonate 25 mEq per liter, glucose was 115 mg per dL, prothrombin time 12.4 seconds and partial thromboplastin time 24.5 seconds. Both the stool and vomitus were 3 plus reactive for blood.

The patient was supported by artificial ventilation via endotracheal tube and was placed on a hypothermic blanket and given intravenous fluids. She remained comatose and continued to bleed at the site of insertion of the endotracheal tube and in the urine. After 5 hours, the fever, coma and bleeding gradually resolved. The patient was fully awake by the 12th hour, was able to walk after removal of the tube and was discharged on the second hospital day.

PATIENT 2. A 19-year-old woman arrived at the hospital in an extremely lethargic state, responding only to very painful stimuli. Within 10 minutes she became severely agitated, spontaneously flailing her arms and legs and continuously screaming. The pupils were dilated and unresponsive to light. There was no nuchal rigidity. The bowel sounds were hyperactive, stools were formed and greenish, and the nasogastric aspirate contained small amounts of blood mixed with food. Blood oozed from venipuncture sites and large bruises formed at sites of trauma. Hemoglobin was 14 grams per dL, packed cell volume 40.8 percent, platelets 186,000 per μL, and leukocytes 21,500 per μL with 80 percent neutrophils, 19 percent lymphocytes and 1 percent monocytes. Prothrombin time was 12.5 seconds, partial thromboplastin time 27.3 seconds. Glucose was 180 mg, creatinine 1.5 mg and blood urea nitrogen 20 mg per dL. Serum sodium was 142 mEq, potassium 4.0 mEq, chloride 110 mEq, and bicarbonate 25 mEq per liter. There was a 4 plus reaction for blood in the urine, and the stool guaiac test reaction was 2 plus. An electrocardiogram showed sinus tachycardia.

Diazepam, 10 mg, was administered intravenously and the patient was packed in ice bags. She began to have many watery greenish stools. She was placed in a quiet dark room and became quieter. Over the next hour she became gradually less responsive and finally only responded to deep pain. The arterial blood pO_2 was 56 mm of mercury, pCO_2 46 mm of mercury, and pH 7.28. Respiratory arrest necessitated intubation and respiratory assistance for 4 hours at which time she began to regain consciousness. Within the next 8 hours the patient recovered fully and was discharged the following day.

PATIENT 3. A 28-year-old woman arrived at the hosiptal vomiting and unable to speak, had an expressionless stare and was unresponsive even to severe pain. The pupils were dilated and fixed and the reflexes were hyperactive. She did not have diarrhea. The hemoglobin was 14.5 grams per dL, packed cell volume 41.2 percent and leukocytes 23,200 per μL with 67 percent neutro-

phils, 1 percent basophils, 36 percent lymphocytes and 6 percent monocytes. The platelets were normal on a blood smear. The prothrombin time was 11.9 seconds, partial thromboplastin time 38.7 seconds and blood glucose 105 mg per dL. The vomitus was positive for blood.

Dextrose and saline solution were administered intravenously. The patient gradually became more responsive. Except for three episodes of brown watery diarrhea and transient writhing dystonic movements, the course of recovery was uneventful. The patient was completely normal after 12 hours and was discharged on the second hospital day.

PATIENT 4. A 33-year-old woman arrived at the hospital unconscious and unresponsive to painful stimuli. She had frothy sputum and vomitus in the mouth, nose and hypopharynx. The vomitus contained small flecks of blood. The pupils were dilated and unresponsive to light. The bowel sounds were hyperactive but there was no diarrhea. The hemoglobin was 13.0 grams per dL, packed cell volume 38.8 percent and white blood cell count 22,300 per μL with a normal differential. Urinalysis showed a 4 plus reaction for glucose and blood. Blood glucose was 204 mg, creatinine 0.7 mg and urea nitrogen 11 mg per dL. Serum sodium was 141 mEq, potassium 3.7 mEq, chloride 103 mEq and bicarbonate 28 mEq per liter. The plasma prothrombin time was 11.6 seconds and partial thromboplastin time 19.3 seconds. The platelets were normal on a blood smear.

The patient vomited in the emergency room, aspirated vomitus and became apneic. Endotracheal intubation and artificial ventilation were instituted and hydrocortisone, 500 mg, and penicillin, 6 million units, were administered intravenously. Blood oozed at venipuncture sites and at the site of insertion of the endotracheal tube. Artificial ventilation was maintained for 2 hours and then terminated when the patient began thrashing about. Bleeding continued for several hours and the tube was removed approximately 8 hours after insertion. She made an uneventful recovery and left the hospital on the third hospital day.

PATIENT 5. A 39-year-old man arrived at the hospital unconscious and unresponsive to pain. He had no gag reflex while vomitus was being suctioned from his mouth and hypopharynx. He was diaphoretic with widely dilated pupils and hyperactive bowel sounds but there was no hemorrhage or diarrhea. The hemoglobin was 15.7 grams per dL, packed cell volume 46 percent, platelet count 294,000 per μL and leukocytes 17,500 per μL with 39 percent neutrophils, 54 percent lymphocytes, 1 percent eosinophils and 6 percent monocytes. Blood urea nitrogen was 22 mg and creatinine 1.4 mg per dL. Serum sodium was 141 mEq, potassium 3.5 mEq, chloride 109 mEq and bicarbonate 20 mEq per liter. Arterial blood pO_2 was 52 mm of mercury, pCO_2 46 mm of mercury, and pH 7.25. Urinalysis showed a 1 plus reaction for ketones and a 3 plus reaction for blood. The vomitus was positive for blood.

After 30 minutes it was easier to arouse the patient from coma. He was increasingly psychotic and had severe visual hallucinations. However, during the next 4 hours he became sleepy and less agitated. He gradually recovered and left the hospital against medical advice 12 hours after admission.

PATIENT 6. A 29-year-old man was unresponsive on arrival at the hospital. Except for blood pressure of 230/130 mm of mercury, dilated pupils and diaphoresis, the results of physical examination were within normal limits. There was no evidence of bleeding. The hemoglobin was 16.4 grams per dL, packed cell volume 46.7 vols percent and leukocytes 17,900 per μL with a normal differential count. The platelets were normal on smear and the prothrombin time was 12.5 seconds. Blood glucose was 142 mg, blood urea nitrogen 19 mg and creatinine 0.8 mg per dL. Arterial pO_2 was 104 mm of mercury, pCO_2 was 28 mm of mercury, and pH was 7.41. The vomitus was positive for blood.

After 40 minutes the patient had gradually become more responsive though he was grossly psychotic, screamed loudly and had severe visual hallucinations. The blood pressure gradually fell to 170/110 mm of mercury over an hour and was 130/70 3 hours after admission. The patient recovered without complication over the next 8 hours and left the hospital the following day.

PATIENT 7. A 28-year-old man walked into the emergency room stating that he thought he had been poisoned. He was belligerent and was having visual hallucinations. Physical examination showed no abnormalities with no evidence of diarrhea or bleeding; however, he subsequently vomited material containing blood. The hemoglobin was 16.3 grams per dL, packed cell volume 47.2 percent and white blood cell count 13,500 per μL with 66 percent neutrophils, 3 percent

basophils, 21 percent lymphocytes and 10 percent monocytes. The platelet count was 458,000 per μL, the prothrombin time was 11.0 seconds and partial thromboplastin time 34.6 seconds. Serum sodium was 140 mEq, potassium 4.3 mEq, chloride 101 mEq, bicarbonate 24 mEq and creatinine 1.4 mEq per liter. Protein was 7.6 grams, albumin 4.6 grams and bilirubin 0.3 mg per dL. Lactic dehydrogenase was 116 international units per liter, glutamic oxaloacetic transaminase 32 IU per liter, creatine phosphokinase 160 IU per liter, glucose 120 mg per dL and alkaline phosphatase 47 IU per liter. The patient refused admission to the hospital and left after 5 hours in the emergency room.

PATIENT 8. A 28-year-old man walked into the hospital complaining of being severely frightened and of having visual hallucinations and "nightmares." Physical examination revealed no abnormalities except for diaphoresis and dilated pupils unresponsive to light. The hemoglobin was 16 grams per dL, packed cell volume 48 vols percent and white blood cell count 23,200 per μL with 86 percent neutrophils, 11 percent lymphocytes and 3 percent monocytes. The prothrombin time was 10.0 seconds and partial thromboplastin time 22.4 seconds. Platelet count was within normal limits. There was a 3 plus reaction for blood in the urine and a 1 plus reaction for protein. The patient remained in the emergency room for several hours, said he felt better and was discharged.

REFERENCES

1. Sunshine I: Handbook of Analytical Toxicology. Cleveland, Chemical Rubber Co, 1969, pp 394-395
2. Mulé SJ: Identification of narcotics, barbiturates, amphetamines, tranquilizers and psychomimetics in human urine. J Chromatogr 39:302-311, 1969
3. Andersen DL: Identification of LSD and other indole alkaloids by ultraviolet degradation products. J Chromatogr 41:491-493, 1969
4. Rubenstein KE, Schneider RS, Ullman EF: "Homogenous" enzyme immunoassay—A new immunochemical technique. Biochem Biophys Res Commun 47:846-851, 1972
5. Fish F, Wilson WD: Excretion of cocaine and its metabolites in man. J Pharm Pharmacol 21 (suppl):135S-138S, 1969
6. Aghajanian GK, Bing OHL: Persistence of lysergic-acid diethylamide in the plasma of human subjects. Clin Pharmacol Ther 5:611-614, 1964
7. Parker KD, Fountan CR, Yee JL, et al: Gas chromatographic determination of ethyl alcohol in blood for medicolegal purposes: separation of other volatiles from blood or aqueous solutions. Anal Chem 34:1234-1236, 1962
8. Hoffer A: D-lysergic acid diethylamide (LSD): A review of its present status. Clin Pharmacol Ther 6:183-255, 1965
9. West LJ, Pierce CM, Thomas WD: Lysergic acid diethylamide: Its effects on a male asiatic elephant. Science 138:1100-1103, 1962
10. Louria DB: Lysergic acid diethylamide. N Engl J Med 278: 435-438, 1968
11. Brawley P, Duffield JC: The pharmacology of hallucinogens. Pharmacol Rev 24:31-66, 1972
12. Andén NE, Corrodi H, Fuxe K, et al: Evidence for a central 5-hydroxytryptamine receptor stimulation by lysergic acid diethylamide. Br J Pharmacol 34:1-7, 1968
13. Boakes RJ, Bradley PB, Briggs I, et al: Antagonism of 5-hydroxytryptamine by LSD 25 in the central nervous system—A possible neuronal basis for the actions of LSD 25. Br J Pharmacol 40:202-218, 1970
14. Martin WR, Sloan JW: Effects of infused tryptamine in man. Psychopharmacologica 18:231-237, 1970
15. Forrer GR, Goldner RD: Experimental physiological studies with lysergic acid diethylamide (LSD-25). Arch Neurol Psychiat 65:581-588, 1951
16. Rinkel M, Hyde RW, Soloman HC, et al: Experimental psychiatry II. Clinical and physio-chemical observations in experimental psychosis. Am J Psychiat 111:881-895, 1955
17. Friedman SA, Hirsch SE: Extreme hyperthermia after LSD ingestion. JAMA 217:1549-1550, 1971
18. Michal F: D-receptor for serotonin on blood platelets. Nature 221:1253-1254, 1969
19. Aledort LM, Niemetz J: Dissociation of platelet aggregation from clot retraction, potassium loss, and adenosine triphosphatase activity. Proc Soc Exp Biol Med 128:658-661, 1968
20. Behnke O: Effects of some chemicals on blood platelet microtubules, platelet shape and some platelet functions in vitro. Scand J Haemat 7:123-140, 1970

Refer to: Fox LP, Weller WJ, Wilder H: Obstetrical caudal anesthesia in a community hospital—A satisfactory plan. West J Med 120:189-192, Mar 1974

Obstetrical Caudal Anesthesia in a Community Hospital

A Satisfactory Plan

LEON PARRISH FOX, MD, WILLIAM J. WELLER, MD, *and*
HELEN WILDER, CRNA, *San Jose, California*

The development of a program to provide complete anesthesia coverage for obstetrics in a community hospital was undertaken as a prospective project which emphasized continuous caudal techniques. Mutually acceptable guidelines were formulated by a group of anesthesiologists and the Department of Obstetrics and Gynecology. A computerized study involving 3,500 labor patients was carried out to thoroughly evaluate the experience over 16 months. The data confirmed the feasibility, safety and wide acceptance of the program. Major complications were few and the anesthesia service to patients was excellent.

OBSTETRICAL PATIENTS desire and deserve safe relief from the major discomforts of labor and delivery. Unfortunately, the perfect anesthesia in this field has not been developed. Obstetricians, by appropriate antenatal conditioning of patients, have been able to provide adequate and acceptable pain relieving techniques for individual parturients. However, there remain some gaps in safety, consistency and overall coverage of anesthesia for obstetrical patients.

One factor contributing to this situation is a shortage of anesthesiologists who are attracted to obstetrical needs, which of course include resuscitation and ventilation of the newborn. This, in turn, adds to the difficulties of providing 24-hour coverage.

Community hospitals of all sizes have always had a serious problem in providing safe obstetrical anesthesia, and the problem remains unsolved. Approximately 10 percent of all maternal deaths and an indeterminate number of perinatal deaths have been attributed to anesthesia causes. Frequently this has been due to the use of untrained personnel.[1]

After several years of observation during which our problem was compounding, interested anesthesiologists and obstetricians consolidated their efforts and developed a plan for full anesthesia

From the Department of Obstetrics and Gynecology, San Jose Hospital and Health Center, San Jose.

Submitted September 17, 1973.

Reprint requests to L. P. Fox, MD, 303 North Fifteenth Street, San Jose, CA 95112.

coverage for obstetrics. It emphasized continuous caudal techniques which became immediately popular. After a good deal of experience with the new program, we determined to evaluate the plan and identify its pluses and minuses by undertaking a thorough study focusing on the safety, effectiveness, acceptability and practicality of our patient care.

Materials and Methods

The San Jose Hospital and Health Center is a complete community hospital of 482 adult beds and 49 bassinets. At the time of this study, it was averaging approximately 220 deliveries each month. The participating staff included 30 obstetricians, 40 generalists and 12 anesthesiologists. The obstetricians accounted for 78 percent of the deliveries. The anesthesiologists provided coverage around the clock and administered all conduction techniques as well as any intravenous or other major general procedures. They employed a Certified Registered Nurse Anesthetist (CRNA) for each eight-hour shift to maintain continuous peridural anesthesia, once it was induced; to administer requested supplementary or emergency inhalation analgesia; to start infusions and to assist in the resuscitation and oxygenization of the newborn. These skilled associates soon became invaluable partners of the labor, delivery and recovery room nurses in the smooth management of the busy delivery suite. They constantly monitored patients in labor, following them through delivery and a minimum of one hour in the recovery room. The anesthesia service was provided for a fee related to how long it took.

A computerized study was undertaken, using information from 3,500 consecutive patients admitted from October 1968 to early March 1970. Collaboration with Hospital Data Processing Consultants resulted in a special protocol programmed to collect pertinent data. It was processed on an IBM 360-30 machine and finally banked on output tape. Six weeks after delivery, the first 567 patients were contacted and asked to complete a questionnaire regarding the acceptability of the anesthesia which they had been given.

A number of the patients received other than continuous caudal anesthesia, the choice depending upon indications and standard obstetrical practice. Some chose "natural" methods of childbirth and, because of the time element, many had no opportunity to receive anesthesia at all (Table 1).

Generally, patients were kept fasting during active labor and those having conduction anesthesia received an intravenous infusion to maintain hydration and provide a conduit for medications, blood or any necessary agents for augmentation of labor. The initial caudal injection was made by the anesthesiologist on his personal choice of patient position, needle or catheter, and agent. Refills were made by the CRNA, when indicated, in a predetermined dosage for the individual patient. During delivery most patients received oxygen by a plastic face mask.

TABLE 1.—*Pain Relief During Labor and Delivery of 3,500 Patients*

Method	*Percent**
Continuous Peridural	89.3
Spinal	7.4
Local, Pudendal, Paracervical, etc.	1.7
Inhalation	6.4
Natural Childbirth	1.7
None, Too Late	1.4

*Includes supplemented failures and combinations.

Deciding just at what stage of labor to begin induction varied with the status of the patient and with our progressing experience. Ideally, the multipara in active labor should have at least 4 centimeters of cervical dilatation with presenting part well engaged, while the primipara should have 5 to 6 centimeters dilatation with descent of the presenting part to the mid pelvis. An obstetrician re-evaluated all patients who did not make progress in labor after two hours of anesthesia.

Standards of obstetrical practice were not interfered with and delivery was usually by outlet forceps. However, a significant number of patients were allowed to deliver spontaneously at the obstetrician's choice.

Results

The acceptance of continuous caudel anesthesia by patients and physicians in our obstetrical practice rapidly progressed from 43 percent in the early months of the program to more than 90 percent today (Table 2). Patients and physicians questioned at the hospital affirmed their satisfaction with the procedure and a poll directed to patients six weeks portpartum indicated continuing preference for this way of managing labor (Table 3). Many patients were satisfied with other types of pain relief and several chose natural methods of childbirth. However, the overwhelming choice was continuous caudal anesthesia for repeated experiences.

TABLE 2.—*Total Number of Patients Receiving Continuous Caudal Anesthesia, 1960-72*

Year	*Deliveries*	*Percent Receiving Caudal*
1960	5,374	43.5
1961	5,737	53.3
1962	5,196	60.3
1963	4,806	68.8
1964	4,099	65.4
1965	3,359	76.2
1966	2,903	80.9
1967	2,880	81.2
1968	2,727	86.8
1969	2,575	88.7
1970	2,553	90.7
1971	1,977	90.9
1972	1,971	93.0
Total	46,157	75.3

TABLE 3.—*Acceptability of Continuous Caudal Anesthesia*

Immediate Interview—2,804 Cases

	Excellent Percent	*Good Percent*	*Fair Percent*	*Unsatisfactory Percent*
Patient	95.2	3.7	.6	.5
Obstetrician	95.5	3.3	.6	.6

Questionnaire Poll Six Weeks Postpartum—567 Patients

	Entirely Satisfactory Percent	*Partly Effective Percent*	*Prefer for Future Percent*	*Never Again Percent*
Patients	79	14	82	7

TABLE 4.—*Caudal Anesthetic Complications*

Type	*Number*	*Percent*
Leg Pains	1,136	39.6
Shivering	238	8.4
Hypotension	63	2.2
Hypertension	17	0.7

Safety

Many reports have indicated the low incidence of obstetric and anesthetic complications with peridural methods when properly administered. Our experience concurs with these views.[2] There were no maternal deaths during this study period. There were 29 newborn deaths, 8.28 per 1,000 live births, and 27 stillborns, none related to anesthesia. These statistics are comparable to those for the previous and succeeding years.

It was our observation that continuous caudal anesthesia significantly lessened the amount of narcotic and other sedative drugs required in labor. Narcotics were used approximately nine times more frequently in patients who did not have caudal anesthesia than in those who did. Apgar scores evaluated independently by the obstetrician and the CRNA were essentially in agreement, and they were usually better for the patients who had caudal anesthesia without premedication. The lower Apgar ratings were usually related to heavy premedication and to obstetrical problems. Fetal bradycardia was rarely noted and then was only transitory. None of the instances in which patients required cesarean section for fetal distress appeared to have cause related to anesthesia.

Complications associated with the anesthetic were not serious (Table 4). Leg pains in varying degrees and of temporary duration occurred in about one third of the patients and were usually relieved by changing of position. Shivering was a most annoying side effect in 8 percent, usually occurring in the air conditioned atmosphere of the delivery room. It was postulated that this was associated with caudal peripheral vasodilatation. Temperature reading showed three times as many of these patients had subnormal temperatures as above normal, and 13 percent had normal readings. The symptom was alleviated by postdelivery injection of meperidine. Breaking of needles, convulsions and urinary retention were extremely rare occurrences.

Of the several anesthetic agents used by the various anesthesiologists, it was finally concluded that lidocaine 1 percent with epinephrine 1: 200,000 was their choice because of its dependability for smooth prolonged action at minimum toxicity. It was also more economical and more appropriately packaged than comparative drugs. Bupivacaine is being used at this time.

Our results agree with those of Bonica and others who have previously reported that uterine contractions and the progress of labor have not been significantly affected by controlled level conduction anesthesia, which is also preferable from the standpoint of oxygenization.[3-5]

Oxytocin was required to augment labor only when the caudal anesthesia was administered too early, when excessive premedication was given and in cases of fetopelvic disproportion or malposition. These are correctable situations which have been extensively investigated and documented by Friedman and Sachtleben.[5] The second stage of labor in our series averaged 43 minutes in primiparas and 36 minutes in multiparas. Of the former 4.6 percent lasted two hours or more and 14 percent of the latter had a duration of an hour or more.

In this series obstetrical complications such as trauma, uterine inertia, postpartum hemorrhage

and prolonged labor were of no higher incidence in patients who received caudal block than in those who did not. Of the caudal group 9.5 percent did have significant lacerations of the birth canal, against 4 percent in the non-caudal group. In our view this reflected the use of the conduction technique in those patients requiring other types of anesthesia for complicated deliveries. Uterine rupture occurred in two cases in which stimulation of labor was invoked without strong reason.

Estimated blood loss was essentially the same in the caudal and non-caudal groups, averaging 225 ml in the former and 250 ml in the latter. Postpartum hemorrhage of greater than 500 ml occurred in 57 patients, and 25 of these received appropriate whole blood transfusions.

Feasibility

Our experience with this plan for 24 hour coverage for obstetrical patients indicates the feasibility of such a plan in a community hospital without benefit of a house staff. That the plan depends on interested anesthesiologists and cooperative obstetricians is obvious. We believe that privately employed certified registered nurse anesthetists in full-time attendence relieve much of burden on the anesthesiologist's time, provide close monitoring of the mother and fetus and guarantee a safer labor and delivery. This technique has been used for more than 13 years and over 34,348 patients have received continuous caudal anesthesia on the obstetrical service.

Effectiveness

This type of anesthesia has long been recognized for its effectiveness in labor and delivery. Failure rates vary with patients and anesthesiologists. Our rate of 3.9 percent compares favorably with those reported by others. Supplemental agents were required in 2.7 percent of the patients in our study.

The duration of anesthesia from the primary induction ranged from 40 to 90 minutes, and the refills were related to the intensity of labor and usually lasted about 45 minutes. There were several cases of unduly prolonged labor which caused criticism of obstetrical judgment. The average total duration of the anesthetic was 4.4 hours. Approximately one-fourth of our patients were able to deliver spontaneously, although usually outlet forceps were used.

With the use of caudal anesthesia the labor suite has become a quiet, calm and pleasant area, with loud reaction to pain a rarity. Precipitous delivery also is rare.

Comment

Although Von Stoekel introduced caudal anesthesia for obstetrical delivery in 1909, it was not widely used until 1942 when Hingson and Edwards published their experience with continuous caudal anesthesia and analgesia methods.[6] With wide experience, most of the drawbacks have been eliminated and safety established with ideal relief of pain in labor and delivery. The difficulties of making this type of anesthesia accessible to all pregnant patients are slowly being overcome.

Before the introduction of the plan for continuous caudal anesthesia on our service, relief of pain in labor and delivery consisted of extensive use of barbiturates, narcotics, scopolamine and the like during the first and second stages of labor. During delivery paracervical, pudendal, local, spinal and single injection caudal anesthesia were used by obstetricians. Frequently, dilute nitrous oxide with oxygen inhalation was administered erratically by the labor nurse, untrained in anesthesia. These practices have been completely eliminated. During our study, 89.3 percent of our patients had continuous caudal infusion and all other patients receiving pain relief obtained it from the trained personnel.

The use of Certified Registered Nurse Anesthetists as aides under direct supervision of the anesthesiologist offers a great opportunity to improve acceptable 24-hour availability of superior obstetric anesthesia. These personnel require the same professional liability coverage at the same rate as the physician, which of course increases the cost of the service.

Our plan is practical with our present obstetric census, but will be jeopardized if total deliveries drop to much lower levels. Consolidating obstetric services into central hospitals could guarantee a more efficient service, including anesthesia.

REFERENCES

1. Cull WA: Twenty-four hour obstetric anesthesia coverage. JAMA 172:416-418, Jan 30, 1960

2. Dogu TS: Continuous caudal anelgesia and anesthesia for labor and vaginal delivery. Obstet Gynecol 33:92-97, Jan 1969

3. Vasicka A, Kretchmer H: Effect of conduction and inhalation anesthesia on uterine contractions. Am J Obstet Gynecol 82: 600-611, Sep 1961

4. Bonica JJ: Obstetric analgesia and anesthesia. NY State J Med 70:2079-2084, Aug 15, 1970

5. Friedman EA, Sachtleben MR: Caudal anesthesia. Obstet Gynecol 13:442-450, Apr 1959

6. Hingson RA, Edwards WB: Continuous caudal anesthesia during labor and delivery. Anesth and Analg 21:301-311, Nov-Dec 1942

Refer to: Kadin MR, Thompson RW: Lymphangiography—Its practical value in surgically staged patients with Hodgkin's disease. West J Med 120:193-199, Mar 1974

Lymphangiography

Its Practical Value in Surgically Staged Patients with Hodgkin's Disease

MICHAEL R. KADIN, MD, *Pasadena,* and RONALD W. THOMPSON, MD, *Los Angeles*

Since the introduction of "staging laparotomy" (to determine the disease's stage) in assessing Hodgkin's disease, some observers have argued that lymphangiography could be safely omitted in the initial diagnostic evaluation.

To test these opinions a series of 75 patients with Hodgkin's disease who had a staging laparotomy and histological correlation with lymphangiograms was reviewed. Of 16 examinations with positive results, one proved to be a false positive. Of the 14 examinations with equivocal results, one proved histologically positive. In the remaining 45 lymphangiograms, five were falsely negative. In all five of these patients abdominal lymph nodes were involved, but in areas that do not routinely opacify on lower extremity lymphangiography. The overall accuracy was 90 percent.

Therapeutically, the lymphangiogram permits accurate planning for treatment by radiation therapy so that all known disease is treated and yet bone marrow is not excessively irradiated. Changes in lymph node architecture after therapy provide valuable information as to regression of the disease or signs of its early recurrence.

When lower extremity lymphangiography was introduced as a routine investigatory device in the early 1960's[1-3] it became possible to determine the stage of Hodgkin's disease with greater accuracy. The retroperitoneal nodes could be more routinely and accurately assessed, appropriately treated with radiation, and evaluated at intervals after the initial therapy. However, after more widespread experience with this diagnostic technique, a number of apparently valid objections were raised as to its value:

- The study may be inaccurate in defining actual involvement in retroperitoneal lymph nodes and does not give any information regarding the porta hepatis nodes, celiac, splenic hilar, or mesenteric nodes.
- The procedure is tedious, time-consuming, expensive, and painful to the patient.
- Ethiodol® emboli almost always occur and

From the Department of Radiological Sciences, Division of Radiation Therapy, University of California, Los Angeles, Center for the Health Sciences.

Submitted, revised, August 14, 1973.

Reprint requests to: M. R. Kadin, MD, Department of Radiation Therapy, Huntington Memorial Hospital, 100 Congress Street, Pasadena, CA 91105.

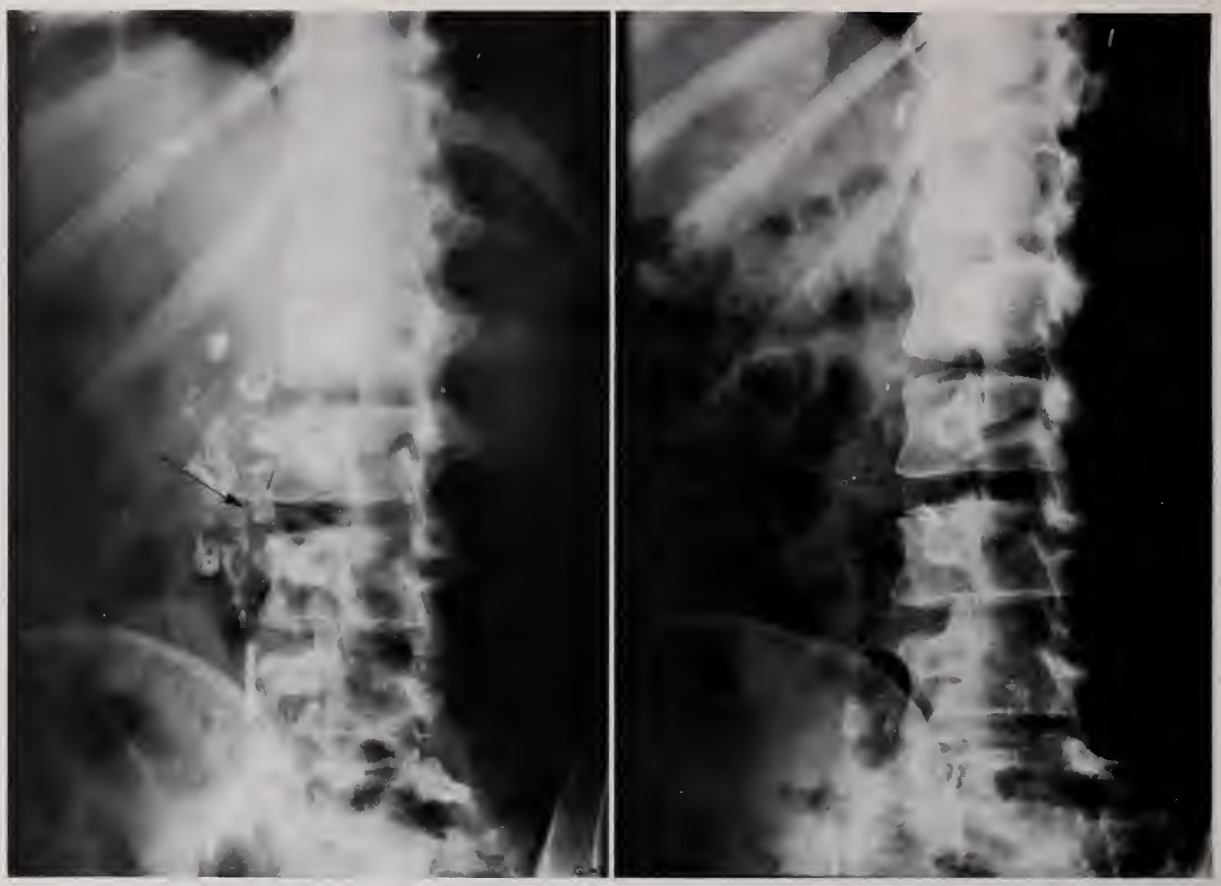


Figure 1.—Left, Preoperative lymphangiogram with arrow indicating several roentgenographically abnormal lymph nodes. **Right,** postoperative film with surgical clips correlating exactly with the abnormal nodes seen on the preoperative film and histologically shown to be involved with Hodgkin's disease.

TABLE 1.—*Staging Laparotomy for Hodgkin's Disease —Results in Abdominal Lymph Nodes, 75 Patients*

Pre-Operative Lymphangiogram		*Histologically Positive*	*Clinical Staging Error*
Positive	16	15	1 of 16 (6%)
Equivocal	14	1	.....
Negative	45	5	5 of 45 (11%)
TOTAL	75	21	6 of 61 (10%)

may cause severe respiratory difficulties in patients with already compromised pulmonary reserve secondary to lymph node disease or underlying respiratory disease.[4-7]

- Allergic reactions to both the vital blue dye and Ethiodol® have been reported.[3]

Isotopic studies such as gallium-67, indium-113m, and gold-198 have been proposed more recently as a substitute for lymphangiography as a diagnostic tool.

Since 1968, the value of a staging laparotomy as a diagnostic tool in the initial investigation of Hodgkin's disease has been explored at various centers[8-14] where histological correlation with the radiographic findings was regularly possible. Early reports from Stanford indicated that lymphangiography was approximately 80 percent accurate in the evaluation of abdominal lymph node disease. Unfortunately, there are a number of physicians involved in treating patients with Hodgkin's disease who have never been convinced of the value of the lymphangiogram and now feel it can be safely omitted[15] from the staging process. The reasons most commonly cited are that lymphangiography is now proven to be unreliable and that the staging laparotomy supersedes the lymphangiogram.

It should be emphasized that the staging laparotomy should still be considered an investigatory tool. It was never intended that it replace the lymphangiogram but rather that it complement it. The objections therefore seem illogical. The purpose of this paper is to clarify and illustrate the role of the lymphangiogram in patients with

Figure 2.—Upper left, preoperative lymphangiogram with arrow showing roentgenographically positive lymph nodes. **Upper right,** the group of three arrows indicates the same roentgenographically positive lymph nodes. Single arrows indicate the biopsy clips. **Left,** four weeks following completion of the abdominal radiation therapy dramatic shrinkage is shown of the roentgenographically positive nodes that were not examined by biopsy (arrow).

Figure 3.—Arrows indicate large radiographically positive nodes not sampled at the time of the staging laparotomy.

Hodgkin's disease and to answer these objections. In addition, several other important uses of lymphangiography will be discussed and illustrated.

Material

At the UCLA Medical Center since 1969, 75 patients with Hodgkin's disease were seen who had lower extremity lymphangiography and histological correlation with a staging laparotomy (Table 1). In this series, lymphangiography correlated with the histological findings in 15 of 16 patients (94 percent) and this was interpreted as demonstrating evidence of Hodgkin's disease. In the 14 patients where interpretation of results was equivocal, the accuracy was less dependable. Of these patients, the result was histologically positive in one (7 percent). This would seem to indicate that equivocal studies are usually negative.

Diagnostic Value of Lymphangiography

The diagnostic inaccuracies of lymphangiography fall into two categories. The first is that regions such as the porta hepatis and epigastric, mesenteric and splenic hilar nodes do not rou-

Figure 4.—The regions within the drawing are those which are irradiated when treating the typical lymph node areas below the diaphragm (inverted "Y") following splenectomy. The surgical clips indicate the splenic pedicle and para-aortic lymph node areas where biopsy specimens were taken.

Figure 5.—A restricted "normal" treatment field as in Figure 4 would not encompass obvious lymph node disease as shown in this lymphangiogram. Arrows indicate extreme lateral displacement of these abnormal lymph nodes.

tinely opacify on lower extremity lymphangiography and therefore cannot be assessed without actual biopsy. This is illustrated (Table 1) by five patients who had a negative lymphangiogram with negative para-aortic lymph node biopsy but had histologically involved lymph nodes elsewhere in the abdomen, splenic hilar lymph nodes in two cases, and in one case each a high abdominal lymph node, a celiac lymph node and a mesenteric lymph node.

The second inaccuracy results when the lymphangiogram is not evaluated before operation. Ideally, the radiologist and the surgeon should discuss the lymphangiogram before operation to delineate the areas that are thought to be involved so that appropriate specimens can be taken for biopsy. This is illustrated in Figure 1. However, when the surgeon takes specimens only from easily accessible para-aortic lymph nodes without consulting the lymphangiogram, a serious diagnostic error may occur. This is illustrated in Figure 2, which shows metallic clips placed in the areas from which specimens were taken. No specimens were excised from the sites that radiographically appeared most abnormal. Although the biopsy of lymph nodes showed no evidence of Hodgkin's disease, it was felt that a sampling error had been made and the patient was treated with radiation to these areas. Subsequently, a dramatic reduction in size of these lymph nodes occurred. To avoid such errors, the lymphangiogram must be seen before surgical operation and discussed in close collaboration with all members of the specialty team.

Another diagnostic use of the lymphangiogram is illustrated in Figure 3. The patient had had a staging laparotomy for Hodgkin's disease at another hospital. A lymphangiogram had not been made preoperatively. The surgical report stated that there were other clinically involved lymph nodes in the abdomen. Because the nature and the extent of the disease were uncertain, the patient had a lymphangiogram which more clearly defined the total extent of disease. This led to more appropriate therapeutic management. It is not possible to rely on an oral or written report by the surgeon based solely on palpation. The lymphangiogram is essential.

Therapeutic Value of Lymphangiography

Lymphangiography has several definite advantages for the radiation therapist. It is estimated that from 50 to 85 percent of the suspect bone marrow may be irradiated with "total nodal" irradiation.[16,17] When the exact extent of disease is not accurately known, larger areas of the body often are irradiated to treat all known and potential disease. The lymphangiogram allows the radiation therapist to plan treatment more precisely and irradiate diseased portions without covering an excessive area (Figure 4). The ability of the patient to tolerate extended field irradiation is in part due to the amount of bone marrow not irradiated. The lymphangiogram permits precise

Figure 6.—Left, preoperative lymphangiogram interpreted as normal. No surgical clips were used. **Right,** the lymph nodes to the left and right of the second lumbar vertebral body have become roentgenographically abnormal by enlargement and displacement. Arrows indicate the nodes which demonstrated the major changes.

and appropriate treatment with definite "bone marrow sparing."

If a patient has extensive abdominal lymph node disease (Figure 5), then treating with "routine" fields of irradiation, as illustrated in Figure 4, would actually miss some of the involved areas. This clearly shows the value of the lymphangiogram in defining the regions to be irradiated.

Follow-up Examination

The Ethiodol® dye usually remains roentgenographically visible in the lymph nodes for periods of from six to eighteen months. By comparison of serial abdominal x-ray films, changes in the lymph node architecture may be seen after radiation therapy. At first abnormal and normal lymph nodes will decrease in size. Subsequent radiographic enlargement of treated lymph nodes may be the first sign of recurrent disease. An example is illustrated in Figure 6. The lymphangiogram was interpreted as roentgenographically normal. This was confirmed by biopsy. Nine months later, a serial x-ray film of the abdomen showed enlargement of several nodes to the left and right of the second lumbar vertebral body. These nodes were proven to be histologically positive.

Repeat lymphangiograms can often be helpful when they are compared with the initial study to evaluate areas that were not involved previously. This is illustrated in Figure 7.

Isotope Studies

New radioisotopic agents are currently being investigated. They also are being used more often in evaluating patients with lymphomatous disease. These radioisotopic agents include gallium-67, indium-113m, and gold-198. Gallium-67 has shown the most promise and has been the agent used most frequently in assessing the anatomic involvement of the disease. A preliminary report by Pinsky[17] has been encouraging. However, experience is too limited at this time to rely exclusively on these agents. They are felt to be an adjuvant to lymphangiography but have not replaced it as a diagnostic procedure.

Conclusions

Some of the objections to performing lymphangiography are valid and the risks involved must be considered. However, the valuable information obtained by such studies outweighs the potential complications. As was clearly shown at the Ann

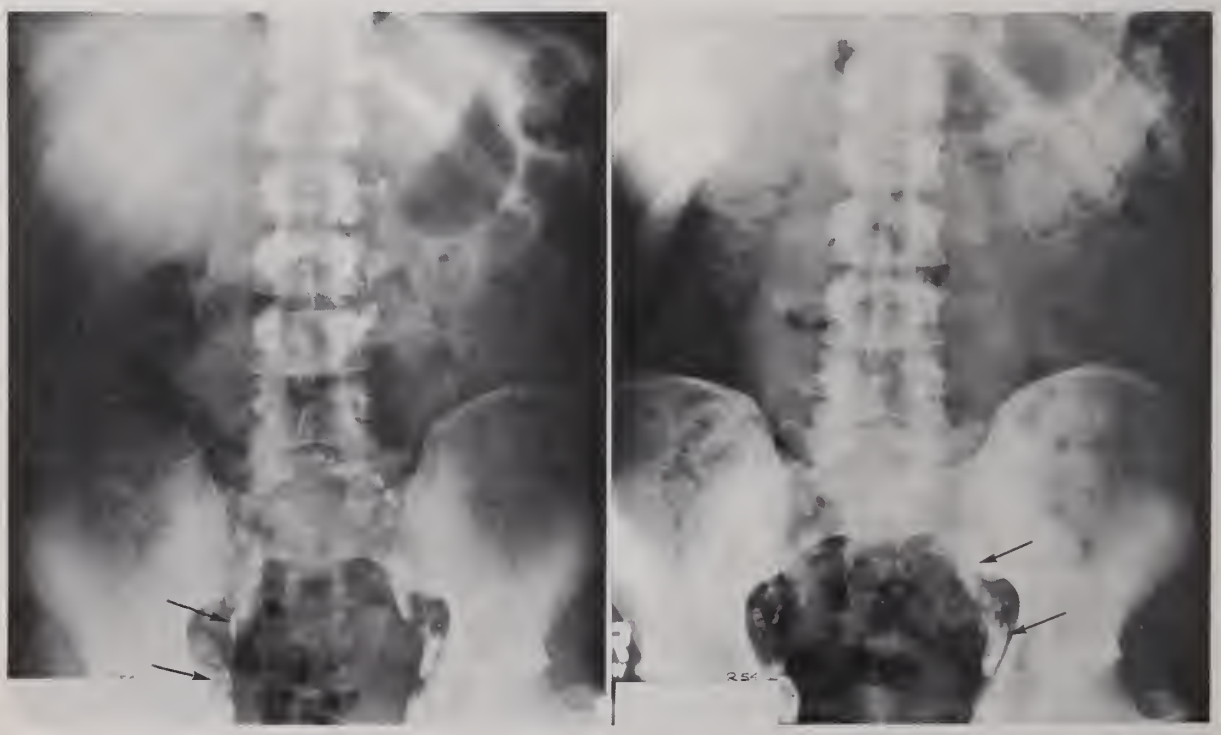


Figure 7.—Left, initial lymphangiogram demonstrated radiographically positive right iliac nodes (arrows). All of the lymph node areas below the diaphragm were irradiated (inverted "Y"). **Right,** two years later, a repeat study was performed because of symptoms suggesting recurrent disease. Radiographically involved left iliac nodes were now shown and confirmed by biopsy.

Arbor Conference on Hodgkin's disease, this procedure may not be safely omitted.[19]

Lymphangiography is of great diagnostic value in detecting para-aortic, iliofemoral, and inguinal lymph node disease. In addition, lymphangiograms have been of great value to radiation therapists in planning the regions of treatment and in follow-up examinations to assess regression or recurrence.

REFERENCES

1. Sheehan R, Hreshehyshyn M, Lin RK, et al: The use of lymphangiography as a diagnostic tool. Radiology 76:417-453, 1961
2. Wallace S, Jackson L, Schaffer B, et al: Lymphangiograms: Their diagnostic and therapeutic potential. Radiology 76:179-199, 1961
3. Viamonte M, Altman D, Parker R, et al: Radiographic-pathologic correlation in the interpretations and lymphangiograms. Radiology 80:903-916, 1963
4. Fraimow W, Wallace S, Lewis P, et al: Changes in pulmonary function due to lymphangiography. Radiology 85:231-241, 1965
5. Clouse ME, Grimsson JH, Wenhind DE: Complications following lymphangiography with particular reference to oil embolization. Am J Roentgenol 96:972-978, 1966
6. Bron KM, Baum J, Abrams HL: Oil embolization in lymphangiography, incidence, manifestations, mechanism. Radiology 80:194, 1963
7. Davidson JW: Lipid embolization to the brain following lymphangiography: case report and experimental study. Am J Roentgenol 105:763, 1969
8. Rosenberg SA, Kaplan HS: Hodgkin's disease and other malignant lymphomas. Calif Med 113:23-38, Oct, 1970
9. Hass AC, Brunk SF, Gulesserian HP, et al: The value of laparotomy and splenectomy in malignant lymphoma. Radiology 101:157-165, 1971
10. Jelliffe AM, Millett YL, Marston JAP, et al: Laparotomy and splenectomy as routine investigations in the staging of Hodgkin's disease before treatment. Clin Radiol 21:439-445, 1970
11. Lowenbraun S, Ramsey H, Sutherland J, et al: Diagnostic laparotomy and splenectomy for staging Hodgkin's disease. Ann Int Med 72:655-663, 1970
12. Prosnitz LR, Nuland SB, Kligerman MM: Role of laparotomy and splenectomy in the management of Hodgkin's disease. Cancer 29:44-50, 1972
13. Ultman JE: Current status: the management of lymphoma. Sem Hematol 7:441-460, 1970
14. Zarembok I, Ramsey HE, Sutherland J, et al: Laparotomy and splenectomy in the staging of untreated patients with Hodgkin's disease. Radiology 102:673-678, 1972
15. Tubiana M: Summary of informal discussion on staging procedures in Hodgkin's disease. Cancer Res 31:1751-1754, 1971
16. Keller AR, Kaplan HS, Lukes RJ, et al: Correlation of histopathology with other prognostic indicators in Hodgkin's disease. Cancer 22:487-499, 1968
17. Woodard HQ, Holodny E: A summary of the data of mechanism on the destruction of human bone marrow. Physics Med Biol 5:57-59, 1960-1961
18. Pinsky SM, Hoffer PB, Turner DA, et al: Place of 67-gallium in the staging of Hodgkin's disease. J Nucl Med 12:385, 1971
19. Rosenberg SA, Boiron M, DeVita VT, et al: Report of the committee on Hodgkin's disease staging procedures. Cancer Res 31:1862-1863, 1971

Graves' Disease: Unusual Presenting Symptoms; Newer Diagnostic Tests

We [ophthalmologists] should tell other specialists who has Graves' disease, not the other way around. Ophthalmologists as a group should not be asking internists and neurologists and neurosurgeons if this patient with eye signs has Graves' disease. We should be telling them . . . Misleading eye signs are (1) isolated unilateral lid retraction . . . in the absence of the more usual concomitants of exophthalmos, congestion and the giveaway stuff that we're all used to seeing . . . ; (2) unilateral exophthalmos—probably a third if not two-fifths of patients with unilateral exophthalmos have Graves' disease . . . ; (3) apparently isolated myopathies [isolated superior rectus palsy, for example].

—Henry J. L. Van Dyk, MD, *Salt Lake City*

Extracted from *Audio-Digest Ophthalmology*, Vol 11, No. 3, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Refer to: Franklin B, Ulmer DD: Human infection with vibrio fetus. West J Med 120:200-204, Mar 1974

Human Infection with Vibrio Fetus

BRUCE FRANKLIN, MD, *and* DAVID D. ULMER, MD
Los Angeles

Vibrio fetus, a slowly growing, microaerophilic, Gram-negative rod which causes infectious abortion in cattle, occasionally induces disease in man. Since persons receiving immunosuppressive agents are among those most susceptible to this infection, recognition of the disease may become increasingly important as transplantation operations increase. Vibrio infections may produce a spectrum of acute and chronic illnesses or may be asymptomatic. Vibriosis may develop at any age but it seems most devastating in the very young or in older debilitated patients. The organism is sensitive to many common antibiotics but has a propensity to produce chronic relapsing illness if treatment is not continued long enough. The method of transmission of the agent is uncertain. Fewer than 100 cases of human vibriosis have been reported, perhaps because of fastidious growth requirements and the initial ease of antibiotic suppression; however, the true incidence of human infection is likely much higher.

VIBRIO FETUS, long known as a causative agent of infectious abortion in cattle, was first recognized to produce human disease in 1947.[1] Since that time, more than 75 cases of local and systemic infection by this organism have been documented in residents from several regions in the United States as well as from abroad.[2-25] Two cases have been reported previously from California.[17,24]

Small infants and elderly adults, as well as patients with chronic debilitating diseases or those receiving immunosuppressive agents, are particularly susceptible to vibriosis. Hence, infections by this organism, like those due to pneumocystis caranii, cytomegalovirus, fungi such as Candida, mucor, and aspergillus, and other "opportunistic invaders" may be expected to become increasingly important wtih the development of transplantation centers and the expanding use of immunosuppressive therapy.

The protean nature of the clinical manifestations of human vibriosis, the propensity for the causative organism to produce a relapsing illness, and the fastidious growth requirements for successful culture of vibrio fetus all suggest that this agent may come to rank among the most troublesome of the opportunistic infections. The recent

From the Department of Medicine, Los Angeles County-Martin Luther King, Jr. General Hospital and the Charles R. Drew Postgraduate Medical School, Los Angeles.

Submitted June 8, 1973.

Reprint requests to: D. D. Ulmer, MD, Department of Medicine, Charles R. Drew Postgraduate Medical School, 1620 East 119th Street, Los Angeles, CA 90059.

observation of a patient with vibriosis cared for at the Los Angeles County-Martin Luther King, Jr., General Hospital and identification of four additional cases by the laboratories at Los Angeles County-University of Southern California Medical Center emphasize these difficulties and prompt the present report.

Reports of Cases

CASE 1. A 67-year-old black male janitor was admitted to hospital 29 March 1972 because of sudden onset of chills, fever and confusion a few hours earlier upon awakening. The patient's wife said that he was a long-standing alcoholic and that he had retired early the previous evening in his usual state of inebriation but without complaining of feeling ill. Past history was notable for a prolonged febrile illness at age 14 diagnosed as rheumatic fever. Seven years before admission he had undergone bronchoscopy and scalene node biopsy because of right middle lobe atelectasis, but no abnormalities were discerned. One year later he was seen at another hospital because of "stress erythrocytosis" and examination showed a red blood cell mass of 35 ml per kg. An intravenous pyelogram showed no abnormality. Four years before admission, peritoneoscopy and liver biopsy showed Laennec's cirrhosis. The patient had resided in the Watts area of Los Angeles since 1943. However, as a youth he lived in Colorado where he frequently worked with cattle. After 1936, he had no significant contact with animals except for a small dog, with which he had slept during the three years before the present admission.

On physical examination the patient appeared acutely ill and emaciated. He had shaking chills and body temperature of 40°C (104°F). Blood pressure was 130/82 mm of mercury and the pulse rate 132. Ecchymosis was present on both forearms. Results of examination of the head, eyes, ears, nose and throat were within normal limits. The neck resisted motion in all planes, but there were no lower extremity meningeal signs. No lymphadenopathy was detected. Fine inspiratory rales were heard over the left lower lung fields posteriorly. The cardiac rhythm was regular; a diffuse apical thrill was accompanied by a Grade III/VI holosystolic murmur radiating into the axilla. The abdomen was soft and the liver edge was percussed 5 cm below the right costal margin.

Leukocytes numbered 23,000 per cu mm with 85 polymorphonuclear cells, 1 band form, and 14 lymphocytes. The hemoglobin was 10.9 grams per 100 ml of blood and the prothrombin time was 25 percent of normal. Blood sugar was 137 mg per 100 ml. The determinations of blood urea nitrogen, serum transaminase (SGOT), sodium, potassium, chloride and carbon dioxide were within normal limits, and a VDRL test was negative. Creatinine was 1.4 mg per 100 ml. The amylase was elevated to 350 international units. Serum electrophoresis showed albumin of 3.1, alpha-1 globulin 0.3, alpha-2 globulin 0.7, beta-globulin 0.9, and gamma-globulin 1.3 grams per 100 ml. A bromsulphalein test indicated only 6 percent retention at 45 minutes. Urinalysis showed a trace of protein. Cardiomegaly was observed on an x-ray film of the chest, and an electrocardiogram showed incomplete right bundle branch block.

Initial attempts to secure spinal fluid and sputum specimens were unsuccessful, and after specimens of blood and urine for cultures had been obtained, both cephalosporin and kanamycin were administered. The body temperature gradually decreased and the patient improved steadily over the ensuing 48 hours. By the fourth hospital day he was afebrile, alert, and oriented. The number of leukocytes had fallen to 10,600 per cu mm. An x-ray film on the fifth hospital day showed a left lower lobe infiltrate and pleural effusion. On thoracentesis 1,100 ml of clear yellow fluid was withdrawn; it had protein content of 1.3 grams per 100 ml and 10 leukocytes per cu mm. No organisms were cultured from the fluid and no malignant cells were identified.

By the tenth hospital day, the patient appeared to have completely recovered from the acute illness, and antibiotics were discontinued. However, on the 13th hospital day the temperature again rose to 39°C (102°F), the patient became disoriented and restless and the white blood cell count increased to 15,000 per cu mm. An x-ray film showed reaccumulation of the left pleural effusion and an additional small effusion on the right. On the same day, the laboratory reported that a very slowly-growing, microaerophilic, Gram-negative rod had been recovered from the initial blood cultures. Urine cultures were negative. Blood cultures were again obtained and ampicillin was administered intramuscularly. Again the patient quickly responded to parenteral antibiotics and, after four days, was able to take oral medication which was continued for the

following two months without evidence of any relapse.

Organisms isolated from cultures of blood at the time of admission and on the thirteenth day were subsequently confirmed as vibrio fetus by the Los Angeles County-University of Southern California Bacteriology Department and by the State of California Department of Public Health. Serum from blood specimens obtained three and a half weeks after onset of the acute illness revealed a vibrio fetus hemagglutination titer of 160 against St. Luke's strain.*

Following are summaries of four additional cases at LA County-USC Medical Center in which positive cultures for vibrio fetus were obtained.

CASE 2. A 30-year-old Hawaiian-Chinese man was admitted 29 May 1971 with cellulitis of the right leg, jaundice and diffuse toxic goiter. Also noted on examination were temperature of 40°C (104°F), rapid atrial fibrillation, hepatomegaly, and congestive heart failure. The hemoglobin was 10.9 grams per 100 ml of blood, and leukocytes numbered 17,900 per cu mm. Tests of thyroid function showed pronounced increase. Despite treatment with sedatives, digitalis, diuretics, and cephalosporin, the patient died on the second hospital day. Vibrio fetus was grown in five days from several blood cultures obtained shortly after admission.

CASE 3. A 20-year-old schizophrenic man who had been admitted previously several times with drug overdose, entered the hospital 26 March 1968 with four days of left lower quadrant crampy pain, bloody diarrhea, and rectal prolapse. Examination showed rectal temperature of 40.6°C, a soft, somewhat tender abdomen with absent bowel sounds and mild rebound tenderness. Hemoglobin content was 17.7 grams per 100 ml of blood and leukocytes numbered 15,500 per cu mm. Abdominal x-ray films showed ileus. The patient was treated with penicillin and streptomycin and the temperature returned to normal in 48 hours. Blood cultures obtained early in the hospital course were reported positive for vibrio fetus after five to twenty-three days of incubation. After nine days of antibiotic treatment in the hospital the patient was discharged and did not return for follow-up examination.

CASE 4. A 21-year-old man was admitted 29 July 1972 with fever, chills and arthralgias of eight hours' duration. Examination revealed fever (38.4°C) and erythema nodosum involving the lower extremities. There were 11,700 leukocytes per cu mm with 59 neutrophils and 26 lymphocytes. Culture of material from the throat grew H. influenza and D. pneumonia. Blood cultures were initially thought to be positive for staphylococcus and the patient was treated with methicillin. He was discharged, well, after ten days. A week later he was readmitted, the organisms in the blood having been further identified as vibrio fetus. At this time, he was asymptomatic. Repeat blood cultures were obtained as well as cultures of cerebrospinal fluid, urine, and sputum. One of ten blood cultures was positive for vibrio fetus. He was treated with tetracycline and streptomycin for six weeks and was still asymptomatic on follow-up examination several weeks later.

CASE 5. A 65-year-old man, a chronic alcoholic, was admitted 19 October 1971 with a ten-day history of diarrhea. On examination he had fever (40°C), rales at the base of the right lung, and atrial fibrillation. Laboratory studies showed elevated blood sugar and changes consistent with chronic liver disease. Cultures of cerebrospinal fluid and urine were negative while the stool was positive for E. coli. Blood cultures showed no growth for two weeks; then vibrio fetus was identified. Administration of antibiotics was begun soon after admission, and at the request of his family, the patient was transferred to another hospital—this before the growth of the organism on the culture. He could not be located on attempts at follow-up.

Discussion

Vibrio fetus was first identified as a disease agent in cattle early in this century and subsequently was recognized as a venereal infection transmitted by the asymptomatic bull. The organism remains indefinitely in the testes and can be cultured from the prepuce and semen of infected animals. It is transmitted to the female during copulation and also through artificial insemination. Although insignificant vaginal lesions are apparent in infected cows, the organism attacks the placenta, causing necrosis and suppuration of the fetal membranes resulting in abortion.[2] In this country, vibrio has come to replace brucellosis as the most common cause of abortion in cattle. More frequently than abortion, however, vibrio causes infertility in heifers.[26] The organism has also been isolated from sheep, but the ram is

*The hemagglutination titer was obtained by Dr. B. Bokkenheuser,[28] St. Lukes Hospital Center, New York.

apparently not involved in sexual transmission of the disease and vibrio is part of the normal intestinal flora in this species. Hence, food and contaminated water are suspected as the source of infection in sheep, as well as in other afflicted species, including goats, pigs, cats, dogs, hamsters, guinea pigs, antelopes, chickens, turkeys and humans.

It has been suggested that sheep are natural carriers for vibriosis and harbor the organisms in the gallbladder. The agent has also been grown from the gallbladder in one case of human infection[20] but the significance of this observation remains uncertain. In this regard, differences in strains may be critical. Innoculation of sheep and cattle with vibrio fetalis variants intestinalis and venerealis results in recovery of intestinalis but not venerealis from both sheep and cattle gallbladders.[25] Significantly, vibrio fetus variant venerealis is the principal agent causing abortion in cattle. However, based on biochemical and serological relationships, organisms from humans have identical characteristics to those of vibrio fetus variant intestinalis, the agent regularly causing abortion in sheep but only occasionally the offender in cattle.[26]

In early laboratory cultures, vibrio appears as a short, comma-shaped, flagellated, Gram-negative rod which becomes spirillar when the cultures are older. The organism is microaerophilic, motile, and non-carbohydrate-fermenting. Cultures are catalase-positive and produce hydrogen disulfide.

In many instances, vibrio can readily be cultured and identified under standard laboratory conditions. Frequently, however, growth is very slow, suggesting an as yet unidentified limiting requirement of the media. Variables which appear to influence the success of cultures include: (1) the size of the innoculum, (2) the precise composition of the media, including the type of blood employed in blood agar plates, and (3) incubation conditions (for example, vibrio grows poorly at 42° in thioglycolate, but well on bovine blood agar at this temperature). It is apparent that very slowly growing cultures of organisms, such as were found in the case presented, would often be discarded prematurely as "negative."

While there is no unmistakable clinical pattern characteristic of human vibriosis, the disease uniformly presents as a febrile infection, usually with shaking chills. Additional manifestations have included dysentery,[17] septic joint,[5,9] endocarditis,[8,14] meningitis,[7] pericarditis,[11] lung abscess,[25] and both upper and lower motor neuron paralysis. In patients with endocarditis, the organisms seem to have a propensity for the aortic valve, although infections of the mitral and tricuspid valves have also been reported.[14] The clinical observations in the present case are consistent with endocarditis of the mitral valve although the heart murmur did not change during hospitalization and peripheral manifestations of endocarditis were absent. Occasionally, the organism produces both deep and superficial thrombophlebitis (even at the sites of venipuncture), which early raised the question of vascular tropism.[2,25]

Since the diagnosis of infection with vibrio may be elusive, repeated cultures from a variety of sources are most likely to yield positive results. However, the organism is seldom cultured from two sources simultaneously. While blood cultures are the most common source of identification, the organism has also been cultured from pericardial fluid,[11] cerebrospinal fluid,[24] brain tissue, placenta, synovial fluid, skin pustules,[13] urine[19] and, rarely, from sources of mixed flora such as the vagina or from milk. Interestingly, no positive stool culture has yet been reported in humans.

In humans the organism is reputed to infect primarily the very young or debilitated older patients, particularly those having diseases which have led to treatment with corticosteroids or immunosuppressive agents. Underlying conditions have included lymphosarcoma, chronic lymphatic leukemia, agammaglobulinemia, cirrhosis, diabetes, chronic alcoholism, and brucellosis.[25,27] Infections have not yet been reported in patients undergoing organ transplantation but they would seem to be a likely susceptible group. Only rarely have cultures been obtained from previously healthy persons, but among patients in whom this did occur were a 45-year-old man with acute dysentery,[17] a laboratory technician with skin pustules,[5] a produce worker,[13] and a 74-year-old woman in whom the agent was found in the common bile duct at the time of cholecystectomy.[20] Occasionally, positive cultures have also been obtained from the mouth and vagina of asymptomatic women during pregnancy, and in neonates.[18] The organism has been cultured frequently from women who have aborted,[3,11,12,18,19] but also from women who have carried an infant successfully to term.[19] In infants, the organism has been found primarily in either blood or cerebrospinal fluid. Two cases have been reported in children with sickle cell anemia.[27] In nine of the total of 71

cases collected by Bokkenheuser,[19] the disease occurred during the perinatal period. Three of the nine infected infants were premature and died. Six were born at term without defects; of these, five survived. Diarrhea and meningitis are the predominant features of all reported neonatal cases.

In the epidemiology of human infections, the importance of animal contact has remained uncertain. In the present case, the only known animal contact was with a small dog; attempts to grow the organism from this animal were unsuccessful. In the series collected by Bokkenheuser, one third of the patients had recent contact with animals or animal products, one third denied such exposure, and in the remainder the history was uncertain. Hence, the source of most human infection remains speculative. Among the possibilities are, of course, direct contact with either infected animals or laboratory cultures, sexual contacts (with the possibility of a dormant state in the testis), and exposure to contaminated water or milk with subsequent infection.[4,12,27] It has also been postulated that vibriosis may be contracted through eating contaminated food, such as raw liver.[27] Placental transfer of the organism or exposure at the time of delivery[18] represents a potential source of infection and it has been suggested that the organism can be contracted *in utero.*[19]

An unusual characteristic of vibrio infections in humans is the chronic nature of the disease; bacteremia of long duration has frequently been reported[2,25] with a striking tendency toward relapse during the weeks or months following discontinuation of initial therapy.[19] This is well illustrated in the present case, relapse occurring after a full ten days of treatment with antibiotics to which the organism was sensitive. In addition to endocarditis or abscess formation, possible mechanisms for such relapse might include the development of *in vivo* resistance, or the appearance of "L forms." The available data do not permit adequate assessment of such alternatives.

Although spontaneous recovery from human vibriosis has been reported,[27] more frequently the course of the illness is chronic or relapsing and requires sustained antibiotic therapy. Fortunately, the agent appears sensitive to most common antibiotics, including tetracycline,[4,27] penicillin,[3,6,19] chloramphenicol,[9] sulfa drugs,[10] erythromycin, colistin, cephalosporin, kanamycin and streptomycin.[19] Only occasional resistance to penicillin and tetracyclinc has been reported.[19] Characteristically, the present patient responded initially to a combination of cephalosporin and kanamycin but, after relapse, responded equally well to treatment with ampicilin. Experience to date suggests that once a clinical response has been obtained to an appropriate antibiotic, therapy should be continued for a prolonged period (at least four weeks) to avoid the possibility of relapse. Even after such prolonged therapy it would seem advisable that, once antibiotics have been discontinued, the patient should be kept under close observation for any evidence of recurrence of the disease.

REFERENCES

1. Vinzent R, Dumas J, Picard N: Septicémie grave au cours de la grossesse due à un vibrion. Avortement consecutif. Bull Acad Nationale Med 131:90-92, Feb 1947
2. Spink WW: Human Vibriosis caused by Vibrio fetus. JAMA 163:180-182, Jan 1957
3. King EO: Human infections with Vibrio fetus and a closely related Vibrio. J Infect Dis 101:119-128, Sep-Oct 1957
4. King EO: Laboratory recognition of Vibrio fetus. Ann New York Acad Sci 98:700-711, Aug 1962
5. Kilo C, Hagemann PO, Marzi J: Septic arthritis and bacteremia due to Vibrio fetus. Am J Med 38:962-971, Jun 1965
6. Jackson JF, Hinton P, Allison F: Human Vibriosis. Am J Med 28:986-994, Jun 1960
7. Collins HS, Blevins A, Benter E: Protracted bacteremia and meningitis due to Vibrio fetus. Arch Intern Med 113:361-364, Mar 1964
8. Loeb H, Bettag J, Yung N, et al: Vibrio fetus endocarditis. Am Heart J 71:381-386, Mar 1966
9. King S, Bronsky D: Vibrio fetus isolated from a patient with localized septic arthritis. JAMA 175:93-96, Mar 1961
10. Kahler RL, Sheldon H: Vibrio fetus infection in man. N Engl J Med 262:1218-1222, Jun 1960
11. Killam HAW, Crowder JG, White AC, et al: Pericarditis due to Vibrio fetus. Am J Card 17:723-728, May 1966
12. Willis MD, Austin WJ: Human Vibrio fetus infection. Am J Dis Child 112:459-462, Nov 1966
13. Lawrence GD, Biggs RD, Woodward TE: Infection caused by Vibrio fetus. Arch Intern Med 120:459-464, Oct 1967
14. Lee MY, Ludwig J, Geraci JE, et al: Fatal Vibrio endocarditis—Report of one case and review of the literature. Virchows Arch Abt A Path Anat 350:87-94, Fasc. 1, 1970
15. Darrell JH, Farrell BC, Mulligan RC: Case of human Vibriosis. Br Med J 2:287-289, Apr 1967
16. White WD: Human Vibriosis—Indigenous cases in England. Br Med J 2:283-287, Apr 1967
17. Mandel AD, Ellison RC: Acute dysentery syndrome caused by Vibrio fetus. JAMA 185:536-539, Aug 1963
18. Eden AN: Perinatal mortality caused by Vibrio fetus. J Pediatrics 68:297-304, Feb 1966
19. Bokkenheuser V: Vibrio fetus infection in man. Am J Epidem 91:400-409, Apr 1970
20. Schwartz R. Hirsch E, Mule J: Antral mucosal diaphragm, clinical and roentgen characteristics, with first reported case of Vibrio fetus in human bile. Am J Gastroenterol 45:366-373, May 1966
21. Cooper IA, Slee KJ: Human infection by Vibrio fetus. Med J Aust 1:1263-1267, Jun 1971
22. McDonald S, Mautner LS: A case of human Vibriosis. Can Med Assoc J 103:951-952, Oct 1970
23. Toala P, McDonald A, Kass EH: Septicemia caused by Vibrio fetus. Arch Int Med 126:306-308, Aug 1970
24. Gunderson CH, Sack GE: Neurology of Vibrio fetus infection. Neurology 21:307-309, Mar 1971
25. Lawrence R, Nibbe AF, Levin S: Lung abscess secondary to Vibrio fetus, malabsorption syndrome and acquired agammaglobulinemia. Chest 60:191-194, Aug 1971
26. White FH, Walsh AF: Biochemical and serological relationships of isolants of Vibrio fetus from man. J Inf Dis 121: 471-474, May 1970
27. Soonattrakul W, Andersen B, Bryner J: Raw liver as a possible source of Vibrio fetus septicemia in man. Am J Med Sci 261:245-249, May 1971
28. Bokkenheuser V: Vibrio fetus infection in man—A serological test. Infect and Immun 5:222-226, Feb 1972

Refer to: Jamison RL: The role of cellular swelling in the pathogenesis of organ ischemia (Medical Progress). West J Med 120:205-218, Mar 1974

Medical
PROGRESS

The Role of Cellular Swelling in the Pathogenesis of Organ Ischemia

REX L. JAMISON, MD, *Stanford*

"The chief point in this application of histology is to obtain recognition of the fact that the cell is really the ultimate morphological element in which there is any manifestation of life and that we must not transfer the seat of real action to any point beyond the cell."[1]

AROUND 1846 RUDOLF VIRCHOW noticed that certain tubular cells of the kidney in Bright's disease contained opaque granules and were swollen, a condition he called "cloudy swelling."[2] From this simple observation, cloudy swelling was later extended to include practically every form of abnormal cell which was either enlarged or contained granules. Cloudy swelling was produced in tissues by various means, including postmortem autolysis, anoxia, starvation, fever, bacteriotoxins, heavy metals, and submerging of tissue in distilled water. Thus as Magno[2] suggested, cloudy swelling may be a mythical entity. Nevertheless, subsequent work has established beyond doubt that when deprived of oxygen or subjected to various insults, cells accumulate fluid and increase in volume. This conclusion was not easily reached, for, as was pointed out by Leaf,[3] the usual methods of dehydration and imbedding of tissues to prepare them for microscopic study so distort cell volume as to make major changes unrecognizable. Even where true cell volume is preserved, an increase of 50 percent in cell volume involves an increase in the radius of individual cells of only 15 percent. With cells cut at various distances from their equatorial plane in histologic section, a change of 15 percent could easily escape detection.

While much work has been done on the mechanisms causing cell swelling, little attention has been paid to its consequences. The purpose of this review is to explore the latter concept. Recent evidence indicates that cell swelling may have profound consequences upon the sequence of events leading to cell damage and death and may be an important mechanism underlying the pathophysiology of temporary ischemia to such organs as the heart, brain and kidney. The implications of these

From the Division of Nephrology, Stanford University Hospital, Stanford, California.

Research by the author reported herein was supported by U.S.P.H.S. NHLI Grant No. HE 11806. Dr. Jamison is the recipient of a U.S.P.H.S. Research Career Development Award 1KO4 HE 42685 and is a Markle Scholar in Academic Medicine.

Reprint requests to: R. L. Jamison, MD, Department of Medicine, Stanford University School of Medicine, Stanford CA 94305.

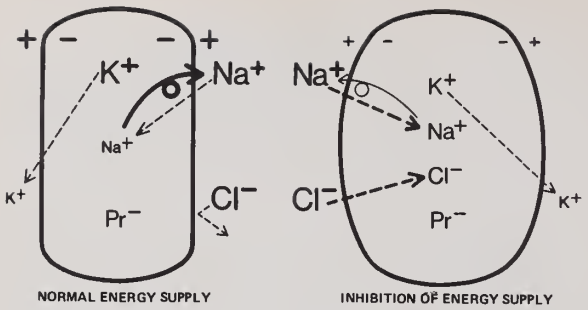


Figure 1.—Sketch of a normal cell **(left)** and swollen cell **(right)** following inhibition of the metabolic supply of energy. In the normal cell operation of the sodium pump (heavy arrow and wheel) maintains a high extracellular sodium concentration which opposes the oncotic pressure exerted by intracellular proteins (Pr^-). The cell interior is shown to be electrically negative compared with the exterior, and to have a high intracellular concentration of potassium. In contrast, chloride is virtually excluded from the cell interior. The dashed lines represent passive movement. Inhibition of metabolic energy reduces the activity of the sodium pump with the result that sodium chloride diffuses into the cell, is followed by water accumulation, and the cell swells. Concomitantly the cell interior becomes less electrically negative and the intracellular potassium concentration is reduced. (After Leaf.[31])

findings may bear upon the treatment of such clinical disorders as ischemic heart disease, cerebral vascular accidents or acute renal failure, and be pertinent to the problem of preservation of organs for transplantation.

Regulation of cell volume

Virchow's view of the cell as a fundamental unit has been borne out by chemical analyses of a variety of cells and tissues.[4] These analyses have revealed a basic characteristic: the internal composition of the cell is fundamentally different from that of the surrounding medium (Figure 1). Cells contain potassium, phosphate and protein in high concentrations, while sodium and chloride are present in very small amounts. The reverse is true of the fluid surrounding the cell. A membrane separating the two solutions must exist because the solutions are aqueous and would otherwise mix. Since the cell is the site of chemical processes which derive their energy from oxidative chemical reactions, the membrane must permit the exchange of materials across it between the internal and external environments. At the same time, in order to maintain the fundamentally different composition of the two environments, the membrane must exhibit selectivity.

A second characteristic of normal cells is that they maintain a constant volume. In the plant kingdom this is achieved by a rigid casing of cellulose, but at the price of immobility.[5] An entirely different solution to maintaining a constant cell volume in the animal kingdom has avoided a rigid cell wall and thus preserved mobility. Virtually all animal cells (with certain important exceptions) are freely permeable to water.[4] A cell and its external environment may be considered to represent a double "Donnan" system in which the cell contains a non-diffusible intracellular anion (protein) whereas all other ions freely permeate the membrane (Figure 1). An extracellular cation, sodium, is excluded from the cell. The osmotic effects of intracellular protein and extracellular sodium with its attendant anion thus counterbalance each other so as to maintain normal cell volume.

Conway and others, using tracers, have shown that the cell is permeable to sodium,[4] so the fact that it is excluded from the cell interior means that as soon as a sodium ion permeates the cell it must be pushed back out again. Thus the mechanism which extrudes sodium from the cell interior acts to maintain intracellular volume and prevent the otherwise disastrous swelling which would occur consequent to the osmotic pressure exerted by intracellular protein. Normally potassium ions enter the cell either by a pump or through other channels driven by the cell electrical potential, for the interior of the cell is electrically negative to its exterior (probably by the action of the sodium pump).

In a steady state, in which potassium influx owing to electrical gradients balances potassium efflux owing to outward diffusion, intracellular potassium concentration is maintained at a high level. The Donnan equilibrium and electrical potential difference account for the virtual exclusion of chloride from the interior of the cell.

As was first shown by Krebs and his colleagues in 1949,[6] maintenance of normal intracellular volume requires energy. They observed that swelling of various tissues *in vitro* was dependent upon tissue respiration; in the absence of oxygen, tissues gained weight due to an increase in water content. Swelling was minimized or prevented by the presence of oxygen. Various inhibitors of oxidative metabolism also produced swelling of cells. Shortly thereafter, Mudge,[7] Leaf[8] and others[3] demonstrated that swelling produced by a variety of inhibitors of metabolism was associated with the uptake of ions as well as water.

If the sodium pump is slowed, for example by

interrupting the energy supply, less sodium will be extruded and sodium will accumulate within the cell (Figure 1). The cell interior will become less electrically negative, allowing potassium to leave and chloride to enter. Osmotic pressure exerted by intracellular colloid will be less strongly opposed by the presence of sodium chloride in the exterior; the cell will accumulate fluid and swell. Fluid entering the cell is similar in composition to the external medium.[8] Resumption of normal metabolic activity within the cell will result in extrusion of sodium and chloride, accumulation of potassium and reduction of tissue hydration.

While the cell regulates its volume by the active extrusion of sodium, there is one type of intracellular volume change to which the cell is highly vulnerable and against which it has no defense: That is the intracellular volume change consequent to changes in osmotic activity of the extracellular fluid. *In vivo*, cells are therefore also dependent for preservation of their volume upon the precision of the regulation by the hypothalamic-hypophysial-renal axis of extracellular fluid tonicity. *In vitro,* cell swelling can be prevented by incubating tissues in fluid containing molecules to which the cell membrane is impermeable (for example sucrose, mannitol or glucose) rather than incubating tissues in isotonic saline alone.[10]

As will be discussed later, some kinds of cells are more susceptible to anoxia (a classic method of disrupting energy supply) than others. Presumably that susceptibility is a reflection of the oxygen requirements characteristic of a given kind of cell. In Table 1 are listed respiratory rates of principal tissues of the body.[11] As can be seen, there is nearly a four-fold variation in the range between the respiratory rate of the retina and that of the skin. These data by themselves, however, are insufficient to account for the sensitivity of various tissues to anoxia. It is also pertinent to inquire as to the energy stores within the cell. Here information is less readily available, but what information exists suggests that the brain[12] is particularly vulnerable to oxygen deprivation.

TABLE 1.—*Respiratory Rates of Principal Tissues of the Body*

Respiratory rate	$-Q_{O_2}$ = *ul* O_2 *per mg dry wt per hr*
Retina	31
Kidney	21
Liver (fasted animal)	17
(fed animal)	12
Jejunum	15
Thyroid	13
Testis	12
Cerebral cortex	12
Hypophysis	12
Spleen	12
Adrenal gland	10
Duodenum	9
Lung	8
Placenta	7
Pancreas	6
Heart	5
Ilium	5
Skeletal muscle	3
Skin	0.8

The Brain and the Discovery of the Impaired-Reflow Phenomenon

In 1963 Ames and Gurian reported some experiments which may be said to represent the initial formulation of the concept of the impaired-reflow phenomenon.[12] They developed a technique to remove the retina, with its optic nerve attached, from an anesthetized rabbit and within 20 seconds immerse it in an oxygenated medium. Retinal function was unimpaired, as judged by the discharge of impulses through the optic nerve evoked by shining light on the retina. Following oxygen deprivation, there was rapid loss of function, ending in complete abolition of the nerve response after three minutes, a time period comparable to the loss of consciousness following circulatory arrest *in vivo*.[13] An unexpected finding, however, was that even though completely deprived of oxygen for periods lasting as long as 30 minutes, the function of the retina was completely restored when oxygen was resupplied to the tissue. Eighty percent recovery from the combined deprivation of both oxygen and glucose was also demonstrable. Recovery of function indicated that the cells were still viable, an observation contrasting sharply with results of clinical resuscitation attempts, which generally fail after a few minutes of anoxia. Whatever the cause of the irreversibility, it was clearly not inherent within the retina. Since the retina is known to possess as high a metabolic rate as any other portion of the nervous system (Table 1), it would seem that the point of no return in an anoxic patient cannot be easily attributed to a characteristic irreversibility of the cells of the nervous system.

It occurred to Ames and Gurian[13] that perhaps the swelling of nervous tissue cells consequent upon oxygen or glucose deprivation may have deleterious effects when it happens *in vivo* within the nonexpansible calverium. Subsequent work[14-20] has shown that while cell swelling may account

for the point of no return, the rigidity of the skull is unlikely to be the reason.

Ames and his collaborators developed a method for producing temporary cerebral ischemia.[17] Rabbits were anesthetized and the basal artery tied and ligated. The animals were allowed to recover and then were observed for seven days, during which they exhibited no apparent neurological deficit. They were re-anesthetized and the common carotid arteries were exposed and temporarily occluded. If the period of ischemia was brief, the animals recovered with no neurological deficit. The maximum period of ischemia after which complete recovery occurred was between 5 and 7½ minutes. Beyond that, death was the rule.

On the theory that the patency of the cerebral vasculature after ischemia might be impaired and that the impairment might account for the irreversibility, two methods were used by Ames et al to determine the patency of the cerebral vessels. By the first method the carotid arteries were perfused with a suspension of fine particles (600 Angstroms diameter) of carbon black at a pressure equivalent to arterial pressure. The brain was removed, fixed in formalin, cut into sections and examined grossly and microscopically for regions of impaired staining by the carbon. In the second method the brain was perfused with Ringer's solution during ischemia to displace intravascular blood. When brains from control animals and from animals made ischemic for only 2½ minutes were perfused with the carbon, all areas of nervous tissue were blackened microscopically; microscopic examination showed that the capillaries were virtually completely filled by the carbon. However, examination of brains subjected to periods of ischemia lasting 5 minutes or more revealed areas not blackened by carbon; the amount of tissue affected by the vascular obstruction increased as the ischemic interval was prolonged, involving as much as 50 to 95 percent of the brain after 15 minutes of ischemia. Pretreatment with heparin provided only slight protection. When the blood was displaced from the brain by flushing with Ringer's solution, post ischemic perfusion with carbon black was complete. Perfusion with a suspension of red cells after ischemia, however, was far from complete, indicating a narrowing rather than complete occlusion of the blood vessels sufficient to block passage of the red blood cells but not the much smaller particles of carbon black.

Ames and his colleagues proposed that this circulatory defect, which they designated the *no-reflow phenomenon*,[18] resulted from a shift of ions and water from the plasma to the perivascular cells leading to an increase in blood viscosity and to a narrowing of the vascular lumen secondary to compression by the swollen cells (Figure 2). (Henceforth we shall refer to the same observation as the *impaired-reflow phenomenon,* a designation which is, strictly speaking, more accurate.) They suggested that this circulatory defect may constitute the first irreversible change in the brain during ischemia, and might be of importance in the pathogenesis of post-ischemic injury to other organs as well. It is particularly noteworthy that the duration of ischemia required for development of obstructive vascular lesions corresponded quite closely with the minimum duration of ischemia necessary to cause death of the rabbits, implying that the vascular changes play a crucial role in determining the point of irreversibility.

In an electron microscopic study of the vascular changes,[15,16,19] the investigators could detect no evidence of fibrin or platelet thrombi in the vessels. With careful fixing techniques, however, perivascular glial cell swelling was demonstrated which was associated with markedly narrowed capillaries (Figure 2b and 2c). A second type of capillary narrowing was caused by the formation of intravascular blebs—blister-like structures arising from the surface of injured capillary endothelial cells (Figure 2c). Similar blebs have been observed by phase microscopy in many types of cells following exposure to a variety of conditions, such as anoxia, toxins, antibody, complement or radiation.[21-23] Sometimes blebbing is so numerous within small vessels as to appear foamy. The foamy contents in glomerular loops described in ischemic kidneys by Sheehan and Davis[24] probably correspond to such a conglomeration of blebs (see below). Morphologic alterations following ischemia similar to those observed by Ames et al were reported by Hills.[14]

Subsequently Cantu and Ames[20] carried out experiments in rabbits to study factors that might prevent the impaired-reflow phenomenon. A hypertonic (20 percent) solution of mannitol was infused into the left ventricle of the heart immediately before occlusion of the cerebral circulation, raising the serum osmolality by 100 to 200 mOsm. Hypertonic (20 percent) glucose was similarly infused in another group of animals, raising the osmolality by 50 to 80 mOsm. In control studies 15 minutes of total ischemia caused ob-

struction such that an average of 50 percent of the brain tissue could not be perfused. Either of the hypertonic solutions completely prevented the obstruction, but an equal volume of isotonic saline solution had no preventive effect. It is interesting that hypercapnia (arterial $pCO_2 = 100\text{-}125$ mm Hg) produced by administering a gas mixture of 20% CO_2, 20% O_2 and 60% N_2 before ischemia, a procedure known to dilate cerebral vessels, greatly reduced the nonperfused areas but did not completely abolish the phenomenon.[20] These findings support the interpretation that obstruction results from a narrowing of the lumen of the microvasculature due to swelling of the endothelial and perivascular cells. The increase in serum osmolality caused by the poorly permeant molecules of glucose or mannitol counteracted the cell swelling, while hypercapnia presumably prevented constriction of the vessels to the critical point that prohibited passage of the red blood cells.[20]

However, it should be emphasized that cell swelling may be only one of several factors underlying the impaired-reflow phenomenon. Fischer and Ames[57] studied the impairment of cerebral circulation in rabbits produced by cross clamping the aorta at its base. Perfusion of the brain with carbon was impaired following total ischemia lasting more than 5 minutes, although not to the extent previously reported by Ames' group, probably because this time they used an aortic catheter for carbon black infusion, whereas in earlier experiments needles of narrower diameter were used which would have reduced the effective perfusion pressure within the intracerebral arteries. The extent of the areas not perfused by carbon black

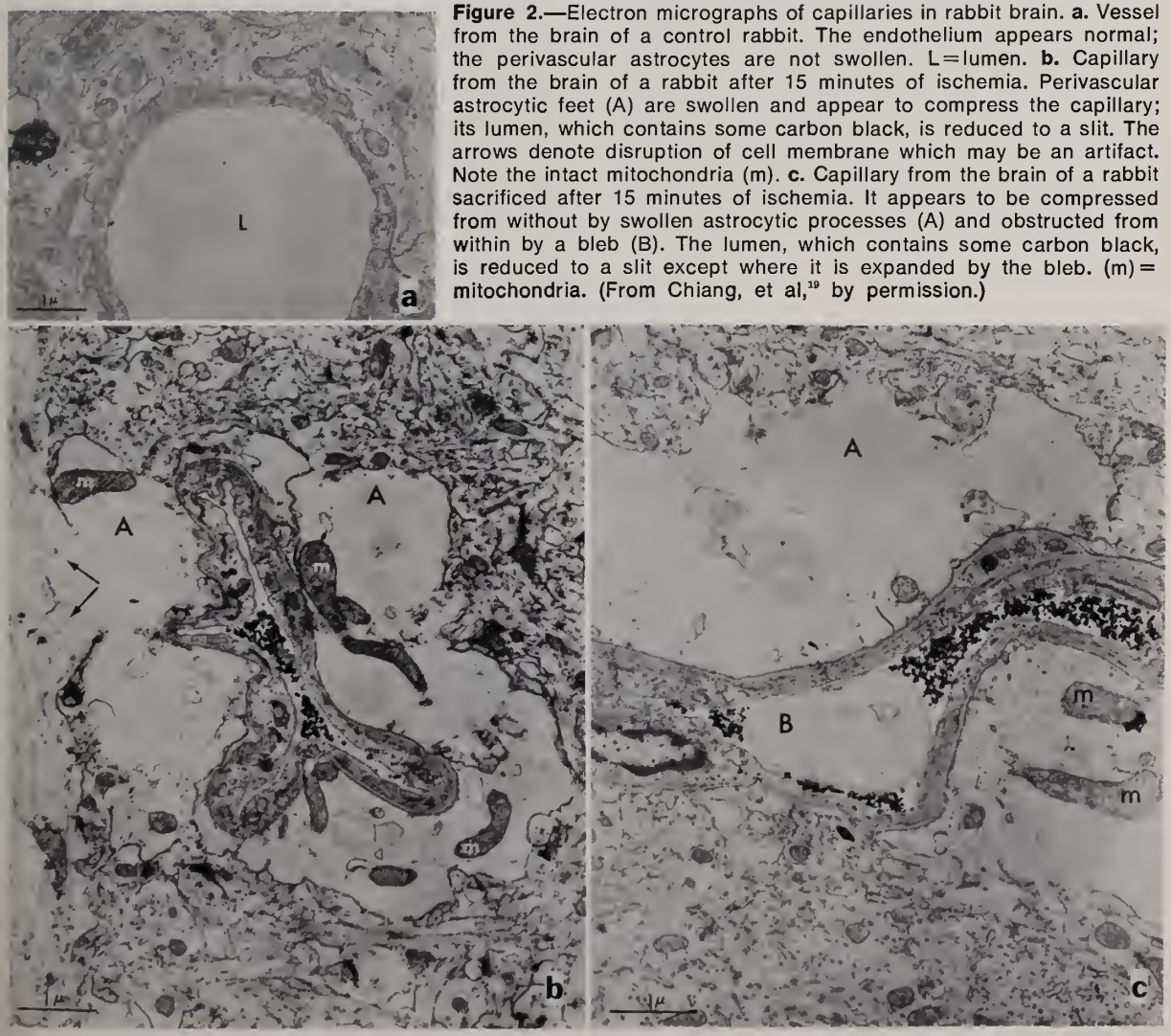


Figure 2.—Electron micrographs of capillaries in rabbit brain. **a.** Vessel from the brain of a control rabbit. The endothelium appears normal; the perivascular astrocytes are not swollen. L=lumen. **b.** Capillary from the brain of a rabbit after 15 minutes of ischemia. Perivascular astrocytic feet (A) are swollen and appear to compress the capillary; its lumen, which contains some carbon black, is reduced to a slit. The arrows denote disruption of cell membrane which may be an artifact. Note the intact mitochondria (m). **c.** Capillary from the brain of a rabbit sacrificed after 15 minutes of ischemia. It appears to be compressed from without by swollen astrocytic processes (A) and obstructed from within by a bleb (B). The lumen, which contains some carbon black, is reduced to a slit except where it is expanded by the bleb. (m) = mitochondria. (From Chiang, et al,[19] by permission.)

after ischemia was inversely related to the perfusion pressure and greatly reduced if the circulating blood was substantially diluted by the intravenous infusion of saline solution before the ischemia. The protective effects of increased perfusion pressure and reduced circulating red cell mass are not easily explained by the theory of intravascular trapping of red cells in capillary lumina narrowed by swollen cells. Fischer and Ames[57] suggested that the increased viscosity of intravascular stagnant blood may play a causal role in the impaired-reflow phenomenon. Merrill and others have shown that blood is a non-Newtonian fluid because, owing to red cell aggregation, its viscosity increases in reduced flow and in no-reflow states; the stress required to reinstitute flow from a state of rest inertia ("yield stress") is a function of the third power of packed red cell volume and the square of plasma fibrinogen (not activated, that is, not fibrin) concentration.[58] Thus the enhanced viscosity of intracerebral blood trapped during the ischemic period may be an important barrier to re-establishing cerebral blood flow following ischemia. This would explain the beneficial effect of acute hemodilution before ischemia, which reduced both red cell volume and fibrinogen concentration, and also why the area of non-perfusion with carbon was reduced at higher perfusion pressures.*

The Impaired-Reflow Phenomenon in the Kidney

Renal Ischemia

Sheehan and Moore[25] have interpreted the histological appearance of renal cortical necrosis in man as indicating the following sequence: A spasm of the renal artery or its main branches lasting three hours or more produces ischemic death of renal tissue. When the spasm is relieved, blood flows into the arteries but is unable to pass through the renal vascular bed and eventually undergoes thrombosis. Sheehan and Davis suggested that the failed reflow of blood accounted for the irreversibility of the lesion. To test this interpretation experimentally they examined sections of kidney tissue after occluding the renal pedicle in rabbits with a clamp.[24,26,27] In these experiments there was evidence that some blood passed *into* the kidney for up to two hours after removal of the pedicle clamp and that a small quantity of blood flowed *through* the kidney for about half an hour but after that circulation ceased. Sheehan and Davis were unable to explain their findings but did observe that even though the larger arteries were wide open after release of the clamp, there was capillary congestion particularly in glomeruli. They also observed "microfoam" in glomeruli,[24] which, as noted above, may actually represent endothelial blebs in glomerular capillary endothelium.[15,16,19]

Stimulated by the findings of Sheehan et al and Ames et al, Summers and I[28] undertook to determine whether the impaired-reflow phenomenon was demonstrable after temporary total renal ischemia. Kidneys of anesthetized rats were exposed and a catheter was inserted in the aorta below the left renal artery. The rats were given heparin intravenously for anticoagulation. Total renal ischemia was accomplished by clamping the renal pedicle for 60 minutes. After release of the clamp, carbon particles suspended in isotonic saline solution were perfused at arterial pressure for ten minutes through the kidneys. Figure 3 shows coronal sections of a series of rat kidneys. The pattern of carbon perfusion in the non-ischemic kidney is shown in Figure 3a. The cortex and medulla were uniformly black. After 60 minutes of ischemia there were reproducible extensive carbon perfusion defects in the cortex and medulla—the impaired-reflow phenomenon (Figure 3c). The size of the defects ranged from punctate carbon-free areas to large wedge-shaped areas involving cortex and medulla. When isotonic saline solution was perfused at arterial pressure to flush out intrarenal blood before clamping, the impairment of carbon perfusion by ischemia was prevented, as illustrated in Figure 3d: the gross appearance of these kidneys was similar to that of control kidneys.

These results indicated that capillaries were sufficiently open in bloodless ischemia to allow passage of the carbon black. However, if blood removed from the rat before the experiment was re-infused into ischemic kidneys emptied of blood by saline solution flushing, carbon perfusion disclosed defects similar in extent to that of ischemic kidneys not flushed beforehand (Figure 3e). These findings demonstrated that reinjected normal blood can reproduce the impaired reflow phenomenon, but they did not indicate to what extent vascular obstruction might result from blood trapped *within the kidney* during ischemia. In this

*A change in intravascular blood viscosity does not, of course, account for the observation that in an ischemic brain emptied of blood by saline solution flushing beforehand, perfusion of a suspension of red blood cells at the end of the ischemic period produces the impaired reflow phenomenon.[18]

regard it should be noted that red cells trapped in capillaries during anoxia are exposed to several factors which might oppose reflow. One of these factors is that rigidity of red cell membranes is increased by adenosine triphosphate (ATP) binding to reduced hemoglobin. Weed et al[29,30] demonstrated increased viscosity and decreased deformability of ATP-depleted red cells and calcium-treated ghost cells (a red cell ghost is a cell in which intracellular hemoglobin has been removed by osmotic shock, leaving only the outside membrane as a transparent envelope). ATP, by binding calcium, maintains normal cell membrane deformability. Should anything (for example, reduced hemoglobin) cause release of this bound calcium, membrane rigidity might be increased. We therefore prepared ghost cells from red cells removed from the rat before the experiment, and treated the cells with calcium to stiffen the cell membranes. The suspension was perfused into kidneys previously flushed with saline solution and made ischemic for 60 minutes. The result was a pronounced decrease in areas stained by carbon, even more so than following injection of normal red cells (Figure 3f).

Other factors which might oppose reflow include fibrin-dependent rouleaux formation,[29] the increase in blood viscosity which occurs when plasma water enters cells in response to anoxic inhibition of the sodium pump[31] (see above), and intravascular coagulation. The importance of clotting is underscored by the fact that in the absence of heparin the same changes occurred after only 15 minutes of ischemia rather than the 60 minutes required in heparinized rats. Heparin may act to prevent the fibrin-dependent rouleaux formation or to prevent the fibrin clots which would contribute to capillary occlusion.

It seemed clear from our experiments that intrarenal capillaries must have been narrowed during ischemia, possibly by swollen ischemic endothelial or tubular epithelial cells, to the extent that red cells trapped within prevented reflow. The demonstration of the impaired-reflow phenomenon in kidneys emptied of blood by saline solution flushing, subjected to 60 minutes of ischemia and then re-perfused with fresh red cells is the key to this conclusion. Here the impaired-reflow phenomenon could not be explained completely by intravascular coagulation, ischemic changes in red cells, or by arteriolar spasm.*

The publication of our findings coincided with

*We attempted to exclude arterial or arteriolar spasm in all our experiments by applying 2 percent procaine to the renal pedicle.

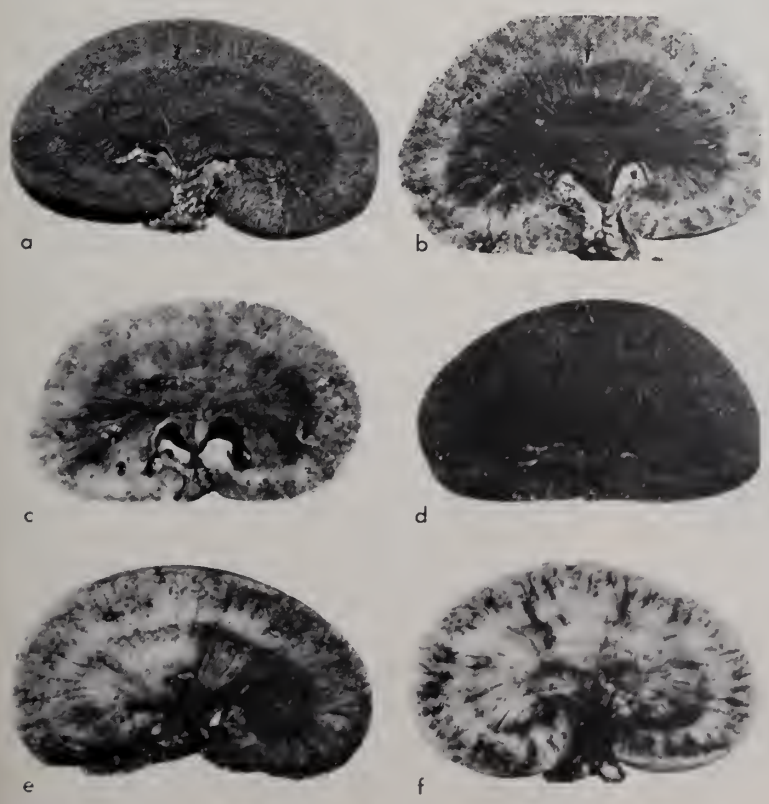


Figure 3.—Coronal sections of rat kidneys, perfused with solution of carbon particles **in vivo**. **a.** Control non-ischemic kidney. **b.** 15-minute ischemia in a rat which was not given anticoagulant. **c.** 60-minute ischemia in a rat given an anticoagulant. **d.** Saline solution perfusion to flush out intrarenal blood followed by 60-minute ischemia. **e.** 60-minute ischemia followed by perfusion with normal red cells. **f.** 60-minute ischemia followed by a perfusion of calcium-treated red cell ghosts. (From Summers and Jamison[28] by permission.)

a report from Leaf's laboratory about the same phenomenon. Flores and colleagues[32] produced renal ischemia in heparinized rats by clamping the renal artery for periods of 60 to 180 minutes. Following the ischemic period, reflow of blood was permitted for intervals of 10 minutes, 30 minutes or 24 hours, after which a silicon rubber suspension was injected via the mesenteric artery to outline the renal vasculature. Figure 4 compares the vascular pattern in the normal control kidney with that seen 10 and 30 minutes after relief of total renal ischemia. In the normal kidney the cortex, subcortex and outer and inner medulla were clearly identifiable. A diffuse patchy ischemia affecting all zones of the kidney was seen after release of the temporary obstruction of the renal artery, even though return of circulation had been permitted for 10 to 30 minutes before injecting the silicon rubber. Figures 3 and 4 show strikingly similar results. To assess the role of red blood cells, additional experiments were performed in which trapped blood was removed from kidneys immediately after clamping the artery by flushing with warm saline solution. When silicon rubber was injected at the end of the ischemic period without permitting blood to re-enter the kidney, the vascular pattern was similar to that in the non-ischemic control kidney. If for 10 minutes reflow of blood into the ischemic kidney was permitted before injection of the silicon rubber, the characteristic patchy vascular ischemia was again seen.

Figure 4.—Vascular pattern of coronal sections of rat kidneys after injection of silicon rubber into the renal artery. Picture at **top** shows the vascular pattern of a normal kidney while the **center** and **lower** kidneys show the vascular pattern after 60 minutes obstruction of the renal artery and 10 or 30 minutes of reflow of the blood through the kidney, respectively, after release of the arterial obstruction. The blood vessels are filled with white silicon rubber and the dark areas represent portions of the kidney which were ischemic. The patchy ischemia in the kidney is evident. (From Flores et al,[32] by permission.)

During ischemia the supply of metabolic energy presumably became insufficient to sustain the usual sodium extrusion rate from the cell and sodium chloride entered the cell, accompanied by water entry, causing the cell to swell. As in the retina experiments, if the energy supply were re-established before the cells die, the process should be reversible and the cell volume should return to normal. Adding mannitol to the extracellular fluid should shrink cells osmotically and prevent their swelling during ischemia, thus keeping capillaries normally patent so that normal blood flow can be re-established before the effects of anoxia become irreversible. To test this hypothesis, Flores et al infused hypertonic mannitol intravenously during the last 15 to 30 minutes of vascular obstruction, which increased plasma osmolality from 304 to 360 mOsm per kg of water. The effect of hypertonic mannitol is shown in Figure 5: the vascular pattern was significantly improved as compared with that observed after ischemia without mannitol.[32] On the other hand the infusion of an even greater volume of isotonic saline solution failed to improve the vascular pattern (Figure 5), suggesting that mannitol exerted its effect osmotically rather than by expansion of the extracellular fluid volume.

Flores and his colleagues[32] examined renal tissue by both light and electron microscopy and found that all types of cells in the ischemic kidney were swollen. The swelling was largely reversed or prevented by hypertonic mannitol (Figure 6). Measurements of the mean endothelial thickness

and of the circumference and area of interstitial cells in electron micrographs confirmed that cell swelling occurred during ischemia and that after hypertonic mannitol the cell measurements were normal.

Both Flores et al and Summers and I[28,32] measured renal function in these experiments. We found that urinary osmolality dropped sharply from 1,500 mOsm to 400 mOsm and gradually returned over the next seven days to pre-ischemic levels. The urinary flow rate and glomerular filtration rate (as measured by inulin clearance) also declined sharply and then recovered over a similar time course.[28] Flores et al[30] found the plasma urea nitrogen increased to 130 mg per 100 ml 24 hours after the period of ischemia.[32]

The question may be asked: How does mannitol exert its effect if the renal vessels into which it is infused are blocked by prior ischemia? As Flores et al stated,[32] not all vessels are totally obstructed after ischemia. Mannitol can penetrate the renal interstitium by diffusing through endothelial cells of patent vessels. The endothelial cells of capillaries exposed to mannitol will be reduced in volume. Neighboring cells will also shrink, releasing obstruction in nearby capillaries so that circulation to the region resumes. The cycle will then repeat itself so that progressively larger areas of ischemic tissue will be exposed to hypertonic perfusate until virtually the entire organ regains its blood flow.

The therapeutic implication for using hypertonic mannitol to disrupt the sequence of events in renal ischemia is clear. Mannitol has been recommended for the treatment of acute renal failure for several years,[33,34] because it was thought to increase the flow of fluid within the tubule lumen, thus avoiding tubular obstruction by casts and debris. The work of Flores et al[32] suggests that its principal effect is dependent upon improving the renal circulation by shrinking ischemic swollen cells.

It should be noted that two recent experiments indicate the need for carefully defining the conditions under which the failed-reflow phenomenon may occur. Daugharty and coworkers[35] studied glomerular dynamics in rats after three hours of nearly complete occlusion of the renal artery in such a way that red cells continued to flow, albeit very slowly, through the capillary circulation. After release of the occlusion, there was a fall in glomerular filtration rate and glomerular plasma flow of single nephrons averaging 39 percent, owing to comparable increases in both afferent arteriolar and efferent arteriolar resistance. The functional consequences of this degree of ischemia were not as severe as those following total renal ischemia, suggesting either that persistent renal blood flow, even though greatly reduced, still pro-

Figure 5.—Vascular pattern of coronal sections of normal kidney at **top** and of kidneys after 60 minutes of obstruction of the renal artery **(second from top)**, 60 minutes of obstruction of the renal artery plus hyperosmotic mannitol **(third from top)** and 60 minutes of arterial obstruction plus a volume of saline solution calculated to expand extracellular fluid volume to a greater degree than the hypertonic mannitol **(bottom)**. The silicon rubber was injected 10 minutes after the release of the renal artery. (From Flores et al,[32] by permission.)

vides sufficient energy to prevent cell swelling from occurring at all or else that cell swelling occurred but was not sufficient to block blood flow completely.

Riley, Alexander and Levinsky[36] studied the failed-reflow phenomenon in the kidneys of dogs before and after 90 minutes of total unilateral renal occlusion. Renal blood flow after occlusion actually increased (as measured by flow meter) whereas the clearances of inulin and para-aminohippurate were reduced by 80 percent. Thus, under these experimental conditions in dogs, the failed-reflow phenomenon did not occur. It seems likely therefore that dog kidney cells are more resistant to ischemic damage than are those in the rat. Nosowski and Kaufman[34] demonstrated that the kidneys in seven out of ten dogs survived clamping the renal artery for two hours when intravenous mannitol was given prophylactically, while the kidneys of only three out of ten dogs not given mannitol survived.

Kidney Preservation for Transplantation

The viable preservation of whole kidneys is an essential component of any transplantation program which does not rely exclusively on a supply of kidneys from living donors. Unless death can be anticipated, it is necessary to store the kidney until accurate matching of donor and recipient can be accomplished. Since these matching procedures are becoming increasingly complex and time consuming, it is necessary to preserve the kidney often

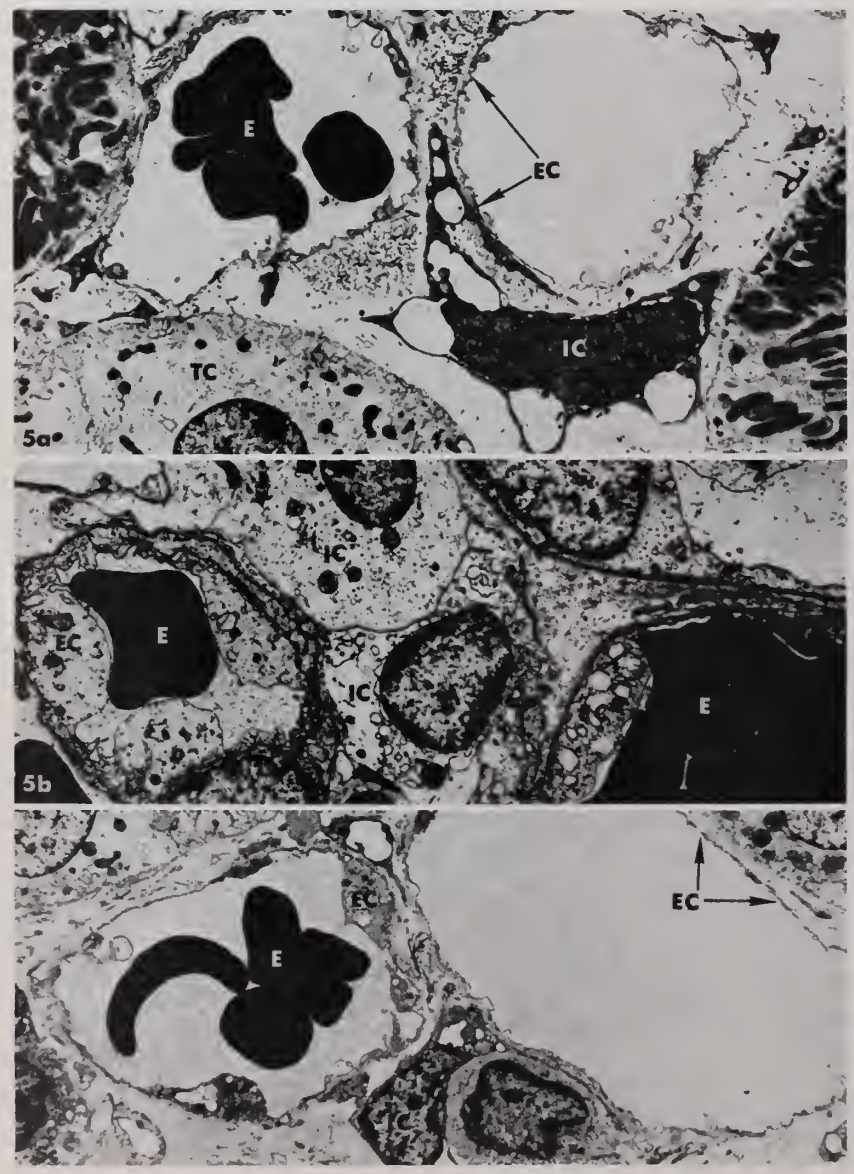


Figure 6.—Electron micrographs from the subcortical zone of normal, ischemic control and mannitol-treated ischemic kidneys. **Upper panel,** Normal kidneys showing patent vessels, flat endothelial cells (EC), an interstitial cell (IC) with a very irregular profile, erythrocyte (E), tubular cell (TC). **Middle panel,** Ischemic kidney with obviously swollen endothelial cells (EC), and interstitial cells (IC). The smaller vessel to the left suggests strongly the role of endothelial swelling restricting blood flow, while larger vessels (a portion of one is seen at the right) are filled with sludged blood. **Lower panel,** Mannitol-treated ischemic kidney. It is evident that the endothelial cells (EC) are flattened approximately as in the normal. The larger vessel, now free of trapped blood, exhibits greater endothelial flattening than the small one. The interstitial cells (IC) appear considerably less swollen than in non-ischemic preparations. All figures are at a magnification of approximately 5,250. (From Flores et al,[32] by permission.)

for as long as three days. The core of the problem of kidney preservation seems to be hypoxia. Hypoxia is followed rapidly by exhaustion of intracellular energy stores, a cessation of the normal metabolic process, and acceleration of catabolic activities.

As Sell[37] has summarized, the two principal approaches to organ preservation are metabolic inhibition and metabolic maintenance. *Metabolic inhibition* can be accomplished by hypothermia[38] or the use of drugs. Hypothermia protects cells by slowing metabolic activity, thus decreasing oxygen need (at 20°C oxygen use is reduced 84 percent, and at 10°C it is reduced by 95 percent of normal[37]). Collins, Bravo-Shugerman and Terasaki[39,40] revived the technique of slowing metabolic activity by hypothermia in experiments in dogs with striking results. As shown by Whittam and Davies,[41] kidney slices gain water and sodium and lose potassium when deprived of oxygen or nutrients or when stored in the cold. Moreover kidneys perfused with cold solutions rapidly lose much of their potassium and magnesium. Collins et al attempted to prevent or minimize these ionic losses during hypothermia by perfusing the extirpated kidneys with a hyperosmotic solution containing high concentrations of potassium phosphate, magnesium sulfate, and glucose. To minimize vasoconstriction owing to autonomic influences and to circulating vasoconstrictive chemicals, they added procaine and phenoxybenzamine to the perfusate. Heparin was also added. Fifteen kidneys were autografted into bilaterally nephrectomized dogs after storage for 8 to 16 hours. All but one of the dogs survived two weeks until sacrifice—and all but one of the survivors had nearly normal serum creatinines. Thirteen dog kidneys were transported by air from Los Angeles to various cities in the United States and transplanted. With one exception, all kidneys functioned well until the onset of rejection.

Simple hypothermic storage alone, however, may not be adequate to preserve cadaver kidneys, especially if the circulation has stopped before the kidneys are removed.[42] As little as 15 minutes of "warm" ischemia (see below) may prevent successful renal implantation, even though the kidneys are preserved according to the Collins technique.

The purpose of metabolic maintenance techniques is to sustain a level of metabolic activity as close to normal as possible.[37] To date, mechanical perfusion of organs *in vitro* has provided the most satisfactory method for storage of human kidneys for clinical transplantation. The best system at present appears to be that of Belzer[43,44] which incorporates a pulsatile pump and homologous plasma passed through a membrane oxygenator. While there are many important factors in mechanical organ perfusion systems, it is clear that the length of time between cessation of renal blood flow to and placement of the kidney in the new environment (ischemic time) is critical, particularly that period of time during which the kidney remains at body temperature ("warm ischemia" time), for the reason that while anoxic damage is readily reversed *in vivo,* it is not easily reversed in even the best perfusion systems. Furthermore while plasma is probably the most physiologically effective perfusate used thus far, the introduction of such agents as mannitol or dextran has been found to prevent kidney cell swelling and subsequent rise in perfusion pressure,[37] an observation closely akin to the impaired reflow phenomenon.

Perhaps the most thorough investigation of changes which occur after perfusion and storage for transplantation is that recently reported by Acquatella, Perez-Gonzales, Moreales and Whittembury.[45,46] Kidneys were removed from anesthetized dogs and the renal arteries catheterized and perfused with 250 ml of a test solution at 4°C under normal arterial pressure until the venous effluent was clear of blood. The kidneys were then immersed in the same test solution at 4°C for 48 hours. Pieces of renal cortex were removed, some immediately and others at 6, 24, and 48 hours thereafter, for tissue analysis and histological studies. With Ringer's solution as the perfusate and bath, there was immediate tissue swelling, with loss of potassium and gain of chloride and sodium. Histological slides showed swollen cells, many of which had ruptured. If hypertonic glucose (200 mM per liter) was added to the Ringer's solution, swelling was prevented to some degree, but cells still lost potassium and gained sodium and chloride. With Collins' fluid the cellular concentration of sodium and chloride remained close to control values, but cell potassium concentration decreased because of cell swelling. In kidneys exposed to a potassium chloride-rich fluid (and hypertonic glucose), the cellular concentrations of potassium and sodium remained close to control values but cells still swelled because of a gain in chloride. Acquatella and his colleagues found that cell swelling could be completely prevented

by the use of a hypertonic glucose solution high in potassium and containing an anion less permeant than chloride—sulfate.[9,48] As the result of these studies, Acquatella et al recommended the following simple hypertonic solution for storing kidneys for transplantation: 60 mM K_2SO_4; 20 mM $NaHCO_3$ and 200 mM glucose.

In summary, successful preservation of kidneys for transplantation depends on the maintenance of a normal cell composition and volume. Several measures, including use of oxygen, hypothermia, mechanical perfusion and a solution designed to minimize shifts in ion and water across cell membranes, appear necessary to accomplish that goal.

The Impaired-Reflow Phenomenon in Muscle

Skeletal Muscle

Volkmann's contracture is a condition in which necrosis of skeletal muscle is followed by fibrosis and contracture.[49] It is commonly a complication of fracture about the elbow in children and involves forearm and hand muscles. The cause has been attributed to obstruction of arterial flow to the extremity.[49] Volkmann himself ascribed the muscle necrosis to ischemia induced by compression of arteries with constrictive dressings.[50] Other investigators suggested that the cause was venous obstruction due to local hematoma or arterial spasm.[50] In 1948 Harman[50] reinvestigated the phenomenon by producing temporary complete ischemia in the right hind legs of rabbits with a tourniquet. Bromphenol blue was used to study the rate of penetration and elimination of small diffusable molecules from ischemic muscle. Immediately after release of the tourniquet the injection of bromphenol blue was followed by rapid intense staining of both normal and ischemic muscles demonstrating that the arteries did not remain occluded. However, when ischemia lasted three hours or more, there was considerable retention of the dye in the muscle, indicating that the circulation was extremely sluggish. After four to six hours of ischemia the dye did not enter the ischemic muscle tissue for at least 30 minutes after the injection. The histologic picture was that of infarction: the capillaries were dilated and engorged with tightly packed erythrocytes. No thrombi were observed. Harman suggested that the probable cause of the sluggish flow through damaged muscles was obstruction in or around capillaries, venules and fine arterioles. Generalized swelling of the involved tissue was documented by the demonstration of a significant gain in weight of the ischemic limb as a function of the duration of ischemia. Recently Strock, Majno and Diethelm demonstrated that perfusion with hypertonic mannitol preserves vascular patency in ischemic dog limbs.[51]

Cardiac Muscle

Krug and coworkers[52] reported that myocardial ischemia is accompanied by a persistent reduction in coronary blood flow even after interrupted blood flow is restored. The effect of restoration of coronary blood flow after temporary ischemia was studied in dogs by Willerson et al,[53] who employed two experimental preparations. In a right heart bypass preparation, the pressure developed by the left ventricle was measured before and after occlusion of the left anterior descending coronary artery. Ventricular function was impaired during ischemia and was significantly improved by the infusion of mannitol. The iso-volumetric canine heart preparation was used to measure total and collateral coronary blood flow, and S-T segment elevation before and during ischemia. Occlusion of the left descending coronary artery brought about pronounced elevation of the S-T segment, and this elevation was significantly reduced by pretreatment with a mannitol infusion. Mannitol also increased total coronary blood flow during ischemia by 150 percent. Collateral coronary blood flow, as estimated by ^{85}Krypton, increased nearly 100 percent during ischemia after pretreatment with mannitol.

These experiments demonstrated that a solution of hypertonic mannitol improved ventricular contractility and reduced S-T elevation during myocardial ischemia and concomitantly caused an increase in total and collateral coronary blood flow into the ischemic region. Such a combination of benefits is unique for mannitol. For example, isoproterenol and digitalis further elevate S-T segments during ischemia. Since it has been demonstrated in the heart that, during ischemia, cellular edema occurs due to failure of the sodium pump,[52,54] ischemia presumably impairs ventricular function by causing myocardial cells to swell. Mannitol probably acted by reducing cell swelling; shrinkage of swollen cells would increase capillary patency and thereby permit increased coronary blood flow to the affected tissue.

The potential clinical usefulness of these studies is uncertain because the exact methods and cir-

cumstances involved in the administration of mannitol to patients with myocardial ischemia have yet to be determined. Nevertheless it would appear that the impaired-reflow phenomenon is characteristic of the myocardium after temporary ischemia and is susceptible to treatment with hyperosmolar agents.

Summary

Several experimental investigations on the possible role of cell swelling in the pathogenesis of organ ischemia suggest that ischemic swelling of cells may constrict capillaries to the point that circulation of the blood does not resume promptly after the cause of the ischemia has been removed, an occurrence referred to as the impaired-reflow phenomenon. The impaired-reflow phenomenon has been demonstrated in brain, kidney, skeletal and cardiac muscle, skin,[55] and adrenal gland[56] in experimental animals. The problems of preservation of kidneys for transplantation may in part reflect the cell swelling occurring during ischemia.

As Leaf[3] has written:

"One cannot but wonder how often such a sequence of self-sustaining changes occurs in tissues leading finally to the death of the tissue. Is the same vicious cycle involved in the development of strokes, whether from arterial sclerosis, cerebral hemorrhage or embolism? Does the ischemia of the myocardium which develops during exertion in people with atherosclerotic coronary vessels interfere with sodium transport and initiate the vicious cycle of cell swelling, vascular obstruction, sustained ischemia with eventual death? Does acute tubular necrosis and renal failure follow transient renal ischemia because of the same sequence of events? Might therapy be effectively directed toward measures which prevent or reverse cell swelling?"

Although the evidence thus far suggests that the answer to these questions is affirmative, much further work needs to be done. Certainly these studies have given new meaning to the axiom of Rudolph Virchow.

REFERENCES

1. Virchow R: Cellular Pathology, 1858, translated from the second edition of the original by Chance F, *In* Clendening L: Source Book of Medical History, New York City, Doner Publications, Inc., 1960, p 624

2. Majno G: Death of liver tissue—A review of cell death, necrosis, and autolysis, chap 20, *In* Rouiller C (Ed): The Liver: Morphology, Biochemistry, Physiology—Vol 2. New York City, Academic Press, 1964, pp 268-313

3. Leaf A: Regulation of intracellular fluid volume and disease. Am J Med 49:291-295, 1970

4. Davson H: A Textbook of General Physiology—Vol 1, 4th Ed, Baltimore, Williams and Wilkins Co., 1970, pp 368-713

5. Leaf A: Maintenance of concentration gradients and regulation of cell volume. Ann N Y Acad Sci 72:396-404, 1959

6. Stern JR, Eggleston LV, Hems R, et al: Accumulation of glutamic acid in isolated brain tissue. Biochem J 44:410, 1949

7. Mudge GH: Electrolyte-water metabolism of rabbit kidney slices: effect of metabolic inhibitors. Am J Physiol 167:206-223, 1951

8. Leaf A: On the mechanism of fluid exchange of tissues in vitro. Biochem J 62:241-248, 1956

9. Whittembury G: Sodium extrusion and potassium uptake in guinea pig kidney cortex slices. J Gen Physiol 48:699-717, 1965

10. Opie EL: The movement of water in tissues removed from the body and its relation to movement of water during life. J Exp Med 89:185-208, 1949

11. White A, Handler P, Smith EL: Principles of Biochemistry, 4th Ed. New York City, McGraw-Hill, 1968, p 346

12. Ames A, Gurian BS: Effects of glucose and oxygen deprivation of function of isolated mammalian retina. J Neurophys 26: 617-634, 1963

13. Heymans C: Survival and revival of nervous tissues after arrest of circulation. Physiol Rev 30:375-392, 1950

14. Hills CP: Ultrastructural changes in the capillary bed of the rat cerebral cortex in anoxic-ischemic brain lesions. Am J Path 44:531-551, 1964

15. Webster H, Ames A: Reversible and irreversible changes in the fine structure of nervous tissue during oxygen and glucose deprivation. J Cell Bio 26:885-909, 1965

16. Majno G, Ames A, Chiang J, et al: No reflow after cerebral ischemia. Lancet 2:569-570, 1967

17. Lowada M, Ames A, Majno G, et al: Cerebral ischemia—An improved experimental method for study; cardiovascular effects and demonstration of an early vascular lesion in the rabbit. J Neurosurg 28:150-157, 1968

18. Ames A, Wright RL, Kowada M, et al: Cerebral ischemia—The no-reflow phenomenon. Am J Path 52:437-453, 1968

19. Chiang J, Kowda M, Ames A, et al: Cerebral ischemia-vascular changes. Am J Path 52:455-476, 1968

20. Cantu RC, Ames A: Experimental prevention of cerebral vasculature obstruction produced by ischemia. J Neurosurg 30: 50-54, 1969

21. Zollinger HU: Cytologic studies with the phase microscope —1. The formation of "blisters" on cells in suspension (protocytosis), with observations on the nature of the cellular membrane. Am J Path 24:545-568, 1948

22. Goldberg B, Green H: The cytotoxic action of immune gamma globulin and complement on Krebs ascites tumor cells—I. Ultrastructural studies. J Exp Med 109:505-510, 1959

23. Bessis M: Studies on cell agony and death in an attempt at classification, *In* DeReuck AVS, Knight J (Eds): Cellular Injury, Boston, Little, Brown, 1964, p 287

24. Sheehan HL, Davis JC: Renal ischemia with failed reflow. J Path Bact 78:105-120, 1959

25. Sheehan HL, Moore HC: Renal Cortical Necrosis and the Kidney of Concealed Accidental Hemorrhage. Springfield, Illinois, Charles C Thomas, 1953

26. Sheehan HL, Davis JC: Complete permanent renal ischemia. J Path Bact 76:569-587, 1958

27. Sheehan HL, Davis JC: Patchy permanent renal ischemia. J Path Bact 77:33-48, 1959

28. Summers WK, Jamison RL: The no reflow phenomenon in renal ischemia. Lab Invest 25:635-643, 1971

29. Weed RI: The importance of erythrocyte deformability. Am J Med 49:147-150, 1970

30. Weed RI, LaCelle PL, Merrill EW: Metabolic dependence of red cell deformability. J Clin Invest 48:795-809, 1969

31. Leaf A: Regulation of intracellular fluid volume and disease. Am J Med 49:291-295, 1970

32. Flores J, DiBona DR, Beck CH, et al: The role of cell swelling in ischemic renal damage and the protective effect of hypertonic solute. J Clin Invest 51:118-126, 1972

33. Barry KG, Cohen A, Knochel JP, et al: Mannitol infusion—II. The prevention of acute functional renal failure during resection of an aneurysm of the abdominal aorta. N Engl J Med 264:967-971, 1961

34. Nosowsky EE, Kaufman JJ: The protective action of mannitol in renal artery occlusion. J Urol 89:295-299, 1963

35. Daugharty TM, Ueki I, Nicholas D, et al: Glomerular dynamics in an experimental model of acute post-ischemic renal failure in the rat. Clin Res 21:227, Feb 1973

36. Riley AL, Alexander EA, Levinsky NG: Effect of ischemia on renal blood flow and distribution in the dog. Clin Res 21:703, Apr 1973

37. Sell KW: Tissue and organ preservation, chap 11, *In* Najarian JS, Simmons RL (Eds): Transplantation, Philadelphia, Lea & Febiger, 1972, pp 404-417

38. Birkeland S, Vogt A, Krog J, et al: Renal circulatory occlusion and local cooling. J Appl Physiol 14:227-232, 1959

39. Collins GM, Bravo-Shugarman M, Terasaki PI: Kidney preservation for transportation—Initial perfusion and 30 hours' ice storage. Lancet 2:1219-1222, 1969

40. Collins GM, Bravo-Shugarman M, Terasaki PI: Kidney

preservation for transportation—II. A simple technique for 12 hour storage and air transport. Transplantation 8:821-828, 1969

41. Whittam R, Davies RE: Active transport of water, sodium, potassium and α-oxoglutarate by kidney-cortex slices. Biochem J 55:880-887, 1953

42. Johnson RWG: The effect of ischemic injury on kidneys preserved for 24 hours before transplantation. Br J Surg 59:765-770, 1972

43. Belzer FO, Ashby BS, Dunphy JE: Twenty-four and seventy-two hour preservation of canine kidneys. Lancet 2:536-539, 1967

44. Belzer FO: Successful 17-hour preservation and transplantation of human cadaver kidneys. N Engl J Med 278:608-610, 1968

45. Acquatella H, Perez-Gonzales M, Morales JM, et al: Ionic and histological changes in the kidney after perfusion and storage for transplantation—Use of high Na versus high K-containing solutions. Transplantation 14:480-489, 1972

46. Whittembury G, Gonzales E, Acquatella H: Kidney preservation. Lancet 1:446-447, Aug 25, 1973

47. Whittenbury G, Proverbio F: Two modes of Na extrusion in cells from guinea pig kidney cortex slices. Pflugers Arch 316:1-25, 1970

48. Dellasega M, Grantham JJ: Regulation of renal tubule cell volume in hypotonic media. Am J Phys 224:1288-1294, 1973

49. Hampton OP, Fitts WT: Fractures and dislocations: general considerations, chap 18, *In* Allen JG, Harkins HN, Moyer CA, et al: Surgery Principles and Practice. Philadelphia, J B Lippincott Company, 1957, p 319

50. Harman JW: The significance of local vascular phenomena in the production of ischemic necrosis in skeletal muscle. Am J Path 24:625-641, 1948

51. Strock PE, Majno G, Diethelm G: Protection of the vascular patency of ischemic dog limbs by various perfusate solutions, *In* Norman J (Ed): Organ Perfusion and Preservation. New York, Appleton, Century & Crofts, 1967, p 27

52. Krug A, de Rochemont W, Korb G: Blood supply of the myocardium after temporary coronary occlusion. Circ Res 19:57-62, 1966

53. Willerson JT, Powell WJ, Guiney TE, et al: Improvement in myocardial function and coronary blood flow in ischemic myocardium after mannitol. J Clin Invest 51:2989-2998, 1972

54. Jennings RB, Sommers HM, Kaltenbach JP, et al: Electrolyte alterations in acute myocardial ischemic injury. Circ Res 14:260-269, 1964

55. Willms-Kretschmer K, Majno G: Ischemia of the skin—Electron microscopic study of vascular injury. Am J Path 54:327-353, 1969

56. Kovacs K, Carroll R, Tapp E: Temporary ischaemia of the rat adrenal gland. J Path Bact 91:235-240, 1966

57. Fischer EG, Ames A: Studies on mechanisms of impairment of cerebral circulation following ischemia: effect of hemodilution and perfusion pressure. Stroke 3:538-542, 1972

58. Merrill EW: Rheology of blood. Physiol Rev 49:863-888, 1969

Headache and Facial Pain

Now what do you do about [cluster headache]? . . . If a patient is willing to get under a hot shower as soon as that pain comes, and the heat of the shower being sufficient to get the head and the trunk red—it may take five minutes, and during that time the headache is much worse—and then turn on the cold. Or, if you've got a cold pool, to have the patient jump in the pool. This, for those who will do it and who will try it, works . . . This is in some way altering autonomic balance. And one other trial, simple though it be, you should not forget: That is, even though it's in the middle of the night, if the person can very promptly, with the onset of the first symptom, take a very hot drink, almost burn his throat, but drink the whole cup, and then put ice in his mouth—and in one in eight or ten, you can abort a case that way. Simple—but it works.

—Augustus S. Rose, MD, *Los Angeles*
Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 6, No. 16, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Refer to: Silvergleid AJ: Thromboembolism—Diagnosis and treatment—Stanford University School of Medicine (Specialty Conferences). West J Med 120:219-225, Mar 1974

Specialty Conference

Chief Discussant

ARTHUR J. SILVERGLEID, MD

Taken from the House Staff Conference held at Stanford University School of Medicine, November 1, 1973

Thromboembolism *Diagnosis and Treatment*

DR. STANLEY L. SCHRIER:* *One of the most difficult clinical problems encountered by general practitioners and internists and referred to hematologists is that of recurrent venous thrombosis and pulmonary embolism. For the past year and a half, Dr. Arthur Silvergleid has been responsible for developing an orderly approach to the diagnosis and management of these patients.*

DR. ARTHUR J. SILVERGLEID:† Thromboembolic disease remains a subject of great interest and concern among practitioners in all fields of medicine. An estimated 50,000 to 100,000 deaths every year in the United States are directly attributable to pulmonary embolization, the major complication of venous thrombosis. Aside from treating the condition itself, the major problem has been in developing a means for accurately diagnosing venous thrombosis before the catastrophic embolus. In addition, until recently an accurate way to assess the value of certain prophylatic measures has been lacking.

Within the past ten years newer diagnostic techniques have been developed, the natural history of thrombotic disease (particularly postoperative veno-occlusive episodes) has been clarified, and various prophylactic and therapeutic programs have been assessed. In our conference this morning we hope to review some of the newer techniques now available, assess their role in the study of prophylactic and therapeutic regimens, and discuss the current status of the management of venous thrombotic disease.

Diagnostic Methods

Clinical Signs

While clinical methods of detecting venous thrombosis have always been suspect, it has now become abundantly clear how inadequate they are. Physical signs of venous thrombosis depend on two aspects of the disease: obstruction, producing signs such as swelling, distension of the veins and increased skin temperature; and phlebitis, producing pain and tenderness. Since most venous disease occurs in the absence of overt signs of inflammation or extensive obstruction, it is not surprising that clinical signs are the exception rather than the rule. When present, however,

*Professor of Medicine, Head, Division of Hematology.
†Fellow in Hematology.
Reprint requests to: S. L. Schrier, MD, Department of Medicine, Stanford University School of Medicine, Stanford CA 94305.

clinical signs have a certain reliability as assessed in a study comparing antemortem findings with necropsy results.[1] Unilateral ankle edema was a reliable sign of underlying venous disease in 80 percent of cases, while tenderness and the Homan's sign were reliable in 50 percent and 8 percent respectively. This inadequacy in the accurate clinical detection of venous disease has been the major stimulus for the development of the other diagnostic techniques we shall discuss.

Phlebography

Developed in the late 1930's, and refined in the 40's and 50's, phlebography is the second oldest and probably the most valuable technique for studying the venous system of the legs. Three methods of phlebography are used most commonly. One is ascending phlebography, in which the injection is made into the dorsum of the foot, with tourniquets used to force the dye into the deep veins of the calf and upper leg. A second is percutaneous femoral phlebography, which is useful if there is an obstruction distal to the common femoral vein. And a third is intraosseous pertrochanteric phlebography,[2] useful in outlining the iliac veins when the common femoral is blocked.

The radiologic diagnosis of venous thrombosis is based on defining a filling defect in an otherwise completely opacified vein. The age of the thrombus can be roughly estimated by ascertaining the degree of adherence of filling defect to the vein wall, the older thrombus becoming totally adherent. To make the diagnosis of obstruction, you must be able to demonstrate the veins above and below the block.

Phlebography is a very valuable technique which is capable of demonstrating 90 to 95 percent of existing thrombi. It is as close as one can approximate a pathologic diagnosis, and is the touchstone with which to judge the accuracy of other methods. In addition to confirming a diagnosis, it accurately pinpoints the site and extent of involvement, and occasionally the age of the thrombus. It is probably the procedure of choice in defining the source of a recent, confirmed pulmonary embolus, and for assessing the "clinically positive" leg. Disadvantages of phlebography include its cost and the fact that it does not well define the soleus plexus of veins in the calf (a potentially important area for the development of postoperative venous thrombosis); it is invasive and almost always results in a transient, mild phlebitis; it cannot be repeated often, a limitation which diminishes its usefulness in evaluating prophylactic measures; and it is not a portable technique. For these reasons, the other techniques we shall discuss were developed.

Doppler Ultrasound Flow Studies

Strandness[3] and Sigel[4] were the first to adapt the principles of ultrasound to the clinical study of venous flow and, concomitantly, venous thrombotic disease. The theoretical basis of this technique is that a beam of ultrasound, when reflected from a moving object, will undergo a frequency shift proportional to the rate at which the object is moving. This frequency shift can be detected by a recorder and transcribed as a dynamic recording of, for example, blood flow in a major vein. By placing the beam and recorder over the femoral vein, and then rapidly squeezing the calf, one can normally detect an augmentation of flow under the probe. A diminution in this "A" wave indicates an obstruction, and theoretically a thrombosis, distal to the beam and probe.

The technique is noninvasive, safe, simple, rapid, cheap and portable. It can quickly show a major obstruction, and is very useful in helping distinguish thrombophlebitis from cellulitis or lymphangitis in an acutely swollen limb. Enthusiasts for this technique report a 75 to 95 percent correlation with venography.[5] Among the disadvantages of the technique are that faulty probe placement, bad leg positioning and failure to keep the legs dependent all can lead to erroneous interpretation of the results. In addition, flow in collateral vessels or a large superficial vein may mimic flow in patent femoral veins and give negative results in the face of clear-cut obstruction. These considerations contribute to the roughly 20 to 25 percent false negative rate associated with the technique. Moreover, ultrasound is of no use in detection of thrombosis in the smaller calf veins or in the pelvis.

Impedance Phlebography

This relatively new technique[6] is based on the theory that the electrical conductivity of the leg varies according to the amount of blood contained, since blood is a good conductor of electricity. An instrument sensitive enough to measure small changes in electrical resistance, therefore, could theoretically measure small changes in blood volume in the leg. Normally a large diaphragmatic inspiratory effort increases the volume of blood in

the leg by increasing the intra-abdominal pressure and decreasing venous blood flow. These venous volume changes associated with respiration are diminished in venous thrombosis and, provided other causes of diminished excursion can be eliminated, the test provides an indirect means of making the diagnosis of obstruction. The test is safe, simple, noninvasive, quick and portable. Unfortunately, venous volume changes can be influenced by a multitude of technical and physiological conditions totally unrelated to venous disease (for example, leg position, breathing mechanics and constrictive clothing). Such conditions contribute to a very high rate of false positives the overall accuracy being 53.5 percent.[7]

Radionuclide Venography

This still developing technique[8-10] is based on the observation that technetium-sulfur labeled macroaggregates of albumin collect at sites of endothelial damage or clot formation to a degree detectable by a scintiscan. Recently, 15μ to 30μ microspheres have been substituted for the often nonspecifically bound macroaggregates, and the specificity of the test has been increased. By using nonrecirculating microspheres labeled with a short lived isotope, it has been possible to combine isotope venography of the limbs with lung scanning in one operation.[10] The virtues of the technique are the ability to visualize the entire venous system from ankle to diaphragm, including the pelvic veins, plus the additional benefit of a simultaneous perfusion scan of the lungs. Correlation with phlebography has been excellent (89 percent). Problems of the technique include its cost, its relative inefficiency in detecting thrombosis in the smaller veins of the calf and the fact that it is not portable. In addition, it does not lend itself easily to use in prospective studies.

Labeled Fibrinogen Uptake

Work by McFarlane[11] indicated that iodinated fibrinogen would clot normally. Based on this research Hobbs and Davies[12] showed in 1960 that ^{131}I-fibrinogen localized in artifically induced thrombi in the hind limb of rabbits. Atkins and Hawkins,[13] in 1965, popularized the technique by switching to ^{125}Iodine, a softer gamma emitter which made it possible to utilize a portable counter. In addition, the longer half life (60 days as compared with eight) of this isotope made it considerably more practical. The technique, as practiced at our institution, involves several processes. First, fibrinogen is purified from the plasma of a single, known HAA-negative donor. The fibrinogen is then radioiodinated with ^{125}I, and the labeled fibrinogen is tested for clottability (aiming for 90 to 95 percent clottability), sterilized by using a millipore filter and stored frozen in 100 microcurie doses. Patients given the isotope have their thyroidal uptake of ^{125}I blocked by daily administration of 150 mg of iodine, as Lugol's solution or saturated solution of potassium iodide, every day for two weeks. After a 100 microcurie dose has been injected intravenously, isotopic counting is done with a Pitman Isotope Localization Monitor 235 at roughly 4-inch intervals along the course of the major veins in the leg. The counts are obtained initially and then daily. They are recorded as percentages of the counts recorded over the heart (to allow for daily decay). A 15 percent difference in any one point on the leg, or at a point on one leg compared with the other, is considered significant.

The technique has several advantages. It is reasonably simple and can be done entirely by a trained technician. It is portable and can be done at the bedside. It also is dynamic—that is, it allows the progression or extension of the thrombus to be followed—and is therefore one of the few techniques of any real value in prospective prophylactic studies. In addition, it is perhaps the only study that is accurate in the soleal plexus of the calf. Correlation with phlebography has been excellent. Most workers would agree that for recent occult and nonocclusive thrombus in the thigh and calf, the ^{125}I-fibrinogen scan is the only reliable screening technique. Our indications for the use of the scan (as distinct from turnover studies) are fourfold: cases of questionable phlebitis, such as tenderness only; cases of suspected, not definite, pulmonary embolus with clinically "silent" legs; cases of known deep venous thrombosis when anticoagulation would be a serious risk and it is important to determine whether the thrombus is really extending cephalad (the importance of cephalad extension will be discussed later); and finally in prospective studies for the evaluation of various prophylactic regimens. The scan is not useful (because of high incidence of falsely positive results) in patients with edema, superficial thrombophlebitis, varicose ulceration, sepsis, flesh wounds or active arthritis.

Disadvantages of the technique, aside from its cost, are the potential for transmitting viral hepatitis (minimized by the use of a single known

TABLE 1.—*Predisposing Factors to Deep Venous Thrombosis in Surgical Patients*

Factor	*Percent of Patients Developing DVT*
1. Surgery (all patients)	30.0
2. Previous pulmonary embolus	100.0
3. Previous DVT	68.4
4. Varicose veins	56.5
5. Obesity	47.9
6. Malignancy	46.7
7. Old age	45.0

Taken from Kakkar et al, Amer J Surg 10/1970

HAA-negative donor) and the fact that it takes roughly 6 to 24 hours before any definite results can be interpreted. In addition, the scan is virtually useless above the upper thigh and in the pelvis, missing completely an area felt by some[14] to be an important source of pulmonary emboli.

Before discussing the natural history and the prophylactic and therapeutic management of thromboembolic disease, I will summarize our general diagnostic approach to the patient with several different clinical patterns. Patients with a major pulmonary embolus who are not candidates for embolectomy (the majority of patients) should probably have phlebography (femoral), or a Doppler study, if that technique is available, to define major obstruction and large residual thrombi. Patients with a proven pulmonary embolus, however minor, should also have phlebographic study of their legs to better define the potential risk of future emboli. Patients with suggestive, but not definite, pulmonary emboli are good candidates for ^{125}I-fibrinogen scanning. For a patient with obvious signs of deep venous thrombosis, there is some debate in the literature as to whether any study is indicated. However, for defining the extent of the thrombus, for assessing its potential for embolization and for determining if there is a need for surgical intervention, phlebography is the most valuable technique. Subtle, or less definite, thrombotic disease is best studied with the fibrinogen scan. Radionuclide venography has not been included in this summary because of its relatively restricted availability.

Natural History of Postoperative Phlebitis, Its Prevention and Treatment

Using the ^{125}I-fibrinogen scan, Kakkar et al[15] studied the natural history of postoperative deep vein thrombosis in a group of 132 patients over the age of 40 undergoing major surgical operations. In that group, 40 patients developed positive scans, 39 of which were confirmed by phlebography. Of the 40 positive scans, 14 lysed spontaneously and 26 remained positive for more than 72 hours. In this latter group, nine of twenty-six extended proximally to the popliteal vein, and four of those nine patients had a pulmonary embolus, thereby defining a high risk group. There were no other emboli in any of the other patients. The importance of cephalad extension of a thrombus is emphasized because this is the group in which anticoagulant therapy is obligatory. In a subsequent study[16] (Table 1) the risk factors in surgical patients were elucidated.

Another critical factor in the natural history of deep venous thrombosis in the postoperative period was pointed out by Flanc et al.[17] They determined that fully one-half of patients who have postoperative thrombosis show an increase in radioactivity over the legs immediately after operation, suggesting that the process probably begins in the operating room.

With the problem thus defined, what has been tried to prevent this 30 to 40 percent incidence of thrombotic disease in such high risk groups as surgical, obstetrical, orthopedic and medical (myocardial infarction) patients? Basically, as it was originally described more than 100 years ago by Virchow, venous thrombotic disease is a function of altered blood coagulability, intimal damage to the vessel wall, or stasis. The major thrust of early studies was to effect a reduction in venous stasis, while most of the more recent work represents an attempt to alter the coagulability of the blood. I will very briefly review some of those studies, and then evaluate the role of heparin as both a prophylactic and a therapeutic agent in venous thrombotic disease.

Although the reports conflict on many points, the consensus of published data indicates that such measures as elevation of the legs, early ambulation and the use of elastic stockings, while decreasing venous stasis, appear to have no influence on the incidence of thrombosis as detected by the ^{125}I-fibrinogen scan. Other methods, such as electrical stimulation[18] or intermittent pneumatic compression of the calf,[19] have resulted in a decrease in positive scans from 35 percent to 5 percent though the incidence of pulmonary emboli has been unaffected. It is argued that the intermittent methods are more effective because they empty the valve cusps of static blood,[20] although such a finding would be difficult to dem-

TABLE 2.—*Major Studies of Low Dose Heparin for Prevention of Postoperative DVT*

Group	Year	No. of Patients	Control Incidence Percent	Treated Incidence Percent	Heparin/ 24 Hr.
Kakkar	1971	53	26	4.0	10,000
Nicolaides ...	1972	244	24	0.8	10,000
Kakkar	1972	78	42	8.0	10,000
Gordon-Smith	1972	150	42	13, 8	10,000
Gallus	1973	226	16	1.9	15,000
Hip fracture		23	48	13.0	15,000

onstrate. In any event, these methods in no way represent a definitive solution.

Anticoagulant Prophylaxis

Acetylsalicylic Acid and Dipyridamole

The approach to prophylaxis via an attack on the coagulability of the blood has taken two main directions: concentration on inhibiting platelet function on the one hand, and a concentration on attempting to prevent the generation of thrombin by using prophylactic doses of heparin on the other. In the first instance, major efforts have been directed toward evaluating acetylsalicylic acid[21] and dipyridamole.[22] In probably the best controlled study, reported by the Steering Committee of the Medical Research Council,[21] the effect of low dose aspirin (600 mg preoperative and then 600 mg every 24 hours) was compared in a double blind fashion with a placebo in 303 patients undergoing major surgical procedures. Despite the fact that an aspirin effect was clearly demonstrable by its influence on measurable platelet function (epinephrine and collagen induced release reaction), there was no difference whatever in the incidence of ^{125}I-fibrinogen detectable thrombosis in either group. An additional, uncontrolled study by O'Brien[23] using 2.4 grams of aspirin per day similarly showed no decrease in the incidence of postoperative thrombosis. These data conflict with a previously published report[24] where low doses of aspirin reduced the incidence of phlebitis in patients undergoing vitallium mold arthroplasty of the hip. The latter study relied on a previous control group, clinical criteria were used to detect thrombosis, and the medication was begun *after* operation (previous studies[17] having shown that thrombosis begins in the operating room in a considerable proportion of cases). A controlled study using dipyridamole alone[22] similarly showed no decrease in the ^{125}I-fibrinogen detectable incidence of thrombosis in the treated group. It would seem reasonable to attempt a controlled clinical trial of the combination of aspirin and dipyridamole before concluding that anti-platelet agents have no role in the prophylaxis of deep venous thrombosis.

Low Dose Heparin

Based upon early studies by Sharnoff,[25] the concept of low dose heparin as a prophylactic agent in postoperative thrombosis was developed and extensively tested in Great Britain and Canada in the past several years.[26-30] These studies are summarized in Table 2. In all of these studies 5,000 units of heparin was administered subcutaneously at eight-hour or 12-hour intervals. Where heparin was administered at 12-hour intervals,[26-29] no heparin effect was detectable by any measurement of coagulation, specifically the thrombin clotting time, although heparin levels were detectable by a sensitive assay.[31] Administration of heparin at eight-hour intervals[30] resulted in slight prolongation of the mean activated partial thromboplastin time (PTT) five hours after the injection. In all studies the patients treated with low dose heparin had a lower incidence of ^{125}I-fibrinogen detectable thrombosis in the calf than the control group. Only in cases of fracture of the femoral neck was low dose heparin ineffective. The only study to show a decrease in the incidence of thrombosis in patients with fracture of the femoral neck was the Canadian study[30] in which, as mentioned, they were able to demonstrate an effect of heparin on the clotting parameters and thus were probably achieving an anticoagulant rather than a purely prophylactic effect. Results similar to those reported for fractures of the femur have also been reported in two major studies of postmyocardial infarction patients.[32,33] In these patients, low dose heparin (7,500 units administered subcutaneously every 12 hours), as compared with untreated control, had no effect whatever on the 25 to 30 percent incidence of ^{125}I-fibrinogen detectable deep vein thrombosis,[32] whereas full heparinization (40,000 units per day by continuous infusion) followed by warfarinization resulted in a decrease to 6.5 percent.[33] The implication in these studies is that for low dose heparin to be effective, it must be administered before any tissue injury. Once there has been tissue injury, as in fracture of the femur or necrosis of myocardial tissue, low dose heparin is ineffective, and conventional anticoagulating levels must be used.

The theory for the effectiveness of low dose heparin as prophylaxis is based partially on work

by Yin and Wessler[34] who were able to demonstrate a naturally occurring alpha two globulin in plasma which functions as an inhibitor to activated Factor X. This inhibitor, alternately referred to as "anti-thrombin III" or "heparin cofactor," is greatly stimulated by low doses of heparin. Factor X stands at the crossroads of both the (so-called) intrinsic and extrinsic pathways of coagulation, and inhibition of the activity of Factor X would therefore prevent the generation of a great deal more thrombin than such low doses of heparin could otherwise neutralize through its purely anti-thrombin activity. Once thrombin is formed, however, (and this is presumed to be the case in the orthopedic and myocardial infarction patients) low dose heparin is of no value. This point, then, is sufficiently important to bear repetition: Low dose heparin appears to have selective use prophylactically, but at present, there is no evidence, either theoretical or clinical, that would indicate any role at all for it in the treatment of established thromboembolic disease.

Is the evidence summarized above sufficiently compelling that all surgical, or potentially bedridden, patients should be placed on prophylactic heparin? This is a very difficult question to answer definitively at this time. In a recent editorial Wessler and Yin[35] noted, after compiling all of the data on the prophylactically treated surgical patients, that there were only five documented episodes of pulmonary embolism in slightly more than a thousand patients. Moreover, three of the five episodes occurred in heparin treated patients. There were no deaths attributable to thromboembolic disease in any of the studies. What they imply is that even were there a definite benefit to the prophylaxis, it would take a massive cooperative study of something like fifty thousand patients in order to approach statistical significance. There is no question that low dose heparin satisfies important criteria such as: lack of important side effects, tolerance by the patients, lack of need for monitoring, other than careful administration and lack of serious bleeding during or after operation. What remains unanswered is whether it will effectively reduce the morbidity and mortality associated with postoperative thromboembolic disease. It is hoped that as a result of larger, controlled, cooperative trials a more definitive answer will be forthcoming.

Heparin as Therapy

The last topic for discussion this morning is the use of heparin in therapeutic doses. In a now classic study[36] in 1960, Barritt and Jordan demonstrated that treatment with anticoagulants (heparin followed by crystalline sodium warfarin—Coumadin®) produced a striking and significant reduction in the incidence of recurrence and death following pulmonary emboli. Although the conclusion has been accepted, there is no uniformly accepted dose or technique for administering heparin. Heparin is usually given either by continuous intravenous drip infusion or by a bolus injected intravenously every four to six hours. Through the years clinicians have vacillated between careful monitoring of coagulation factors (for example, Lee White clotting time, PTT) or merely selecting an arbitrary dose for the 24-hour period and not monitoring the effect of that dose. One recent study[37] attempted to monitor the effect of continuous heparin on the activated partial thromboplastin time and was able, I think, to correlate recurrences and excessive bleeding in a convincing way to the degree of prolongation of the PTT.

Clearly, the bolus technique of administering heparin has several distinct advantages: it is more convenient, it is less subject to variation in terms of how fast the infusion is run in (a problem with the continuous method) and patients have more mobility as the acute phase of their disease subsides. What is not clear, however, is whether there are significant disadvantages of that mode of administration that outweigh the relatively modest advantages. Specifically does bolus therapy subject the patient to greater risk of hemorrhage during the time after the bolus when the clotting time is apparently infinite? And is the thrombus more liable to extend during the short time before a bolus is given, when there may be no measurable anti-coagulant effect? These are the specific questions we are trying to answer in our current study of the use of heparin in thromboembolic disease.

For the study, patients with proven deep vein thrombosis have been divided randomly into two groups and receive one of two modes of therapy. One group receives heparin continuously through a constant infusion pump at a level to prolong the activated PTT to between one and one-half to two times control. The second group receives a bolus of heparin every four hours with the aim of prolonging the PTT to one and one-half times control

at three and one-half hours after the bolus. We are planning to use the ^{125}I-fibrinogen scan in all patients as a means for determining the adequacy or efficiency of therapy. For example, continued deposition of fibrinogen or extension of the thrombus cephalad will be considered a failure of that particular method of administration, or that dose level. With the help of this new diagnostic tool, we hope soon to have some interpretable data showing the best means of treating an old, though still formidable, disease.

Question from the Audience

• Could you please comment on an article in the *Lancet* approximately a year ago which found the ^{125}I-fibrinogen scan to be not useful in patients with pulmonary emboli.

DR. SILVERGLEID: That particular article[38] raises, I think, more questions than it answers. At the heart of the problem, both in understanding and accepting the results of the study, is a major controversy in the literature as to where the potential embolus arises. Is the peripheral segment or the iliofemoral segment, the pathologically more significant source of pulmonary emboli? The authors of this particular study firmly believe that iliofemoral thrombosis is more significant. Therefore they are convinced that the ^{125}I-fibrinogen technique is not a useful tool in terms of predictably preventing pulmonary emboli.

In addition, there are several problems with their technique. In their methods, they do not mention whether or not their labeled fibrinogen is clottable, and therefore useful. And more than half of their patients also had negative venograms, suggesting that the original diagnosis may be questionable. Most workers who use the labeled fibrinogen claim that it incorporates only into forming, and not already formed, thrombi. These workers would agree that in patients who already have experienced a pulmonary embolus, and who may have old thrombus as the source, the labeled fibrinogen scan is not the procedure of choice. This, I feel, in no way detracts from its usefulness in studying the effects of prophylaxis, or in dynamically following the progression or extension of a thrombus.

REFERENCES

1. McLachlin J, Richards T, Paterson JC: An evaluation of clinical signs in the diagnosis of venous thrombosis. Arch Surg (Chicago) 85:738-744, 1962
2. Thomas ML, Fletcher EWL: The techniques of pelvic phlebography. Clin Radio 18:399-402, 1967
3. Strandness DE, Schultz RD, Sumner DS, et al: Ultrasonic flow detection. A useful technique in the evaluation of peripheral vascular disease. Am J Surg 113:311-320, 1967
4. Sigel B, Pupky GL, Wagner DK, et al: Comparison of clinical and Doppler ultrasound evaluation of confirmed lower extremity venous disease. Surgery 64:332-338, 1968
5. Strandness DE, Sumner DS: Ultrasonic velocity detector in the diagnosis of thrombophlebitis. Arch Surg 104:180-183, 1972
6. Wheeler HB, Pearson D, O'Connell D, et al: Impedance phlebography. Arch Surg 104:164-169, 1972
7. Dmochowski JR, Adams DF, Couch NP: Impedance measurement in the diagnosis of deep venous thrombosis. Arch Surg 104:170-173, 1972
8. McDonald GB, Hamilton GW, Barnes RW, et al: Radionuclide venography. Nucl Med 14:528-530, 1972
9. Webber MM, Winona V, Cragin MD: Demonstration of thrombophlebitis and endothelial damage by scintiscanning. J Nucl Med 100:93-97, 1971
10. Yao JST, Henkin RE, Conn J, et al: Combined isotope venography and lung scanning. Arch Surg 107:146-151, 1973
11. McFarlane AS: Labelling of plasma proteins with radioactive iodine. Biochem J 62:135-143, 1956
12. Hobbs JT, Davies JWL: Detection of venous thrombosis with ^{131}-labelled fibrinogen in the rabbit. Lancet ii:134-135, 1960
13. Atkins P, Hawkins LA: Detection of venous thrombosis in the legs. Lancet ii:1217-1219, 1965
14. Mavor GE, Galloway JMD: The iliofemoral segment as a source of pulmonary emboli. Lancet i:871-874, 1967
15. Kakkar VV, Flanc C. Howe CT, et al: Natural history of postoperative deep-vein thrombosis. Lancet ii:230-232, 1969
16. Kakkar VV, Howe CT, Nicolaides AN, et al: Deep vein thrombosis of the leg. Am J Surg 120:527-530, 1970
17. Flanc D, Kakkar VV, Clarke MB: The detection of venous thrombosis of the legs using ^{125}I-labelled fibrinogen. Br J Surg 55:742-747, 1968
18. Browse NL, Negus D: Prevention of postoperative leg vein thrombosis by electrical muscle stimulation—An evaluation with ^{125}I-labelled fibrinogen. Br Med J 3:615-618, 1970
19. Hills NH, Pflug JJ, Jeyasingh K, et al: Prevention of deep vein thrombosis by intermittent pneumatic compression of calf. Br Med J 1:131-135, 1972
20. Browse N: Advances in management of deep vein thrombosis. Modern Medicine, Sep 3, 1973, p 27-32
21. Report of the Steering Committee, Butterfield WJH, Chairman: Effect of aspirin on postoperative venous thrombosis. Lancet ii:441-444, 1972
22. Browse NL, Hall JH: Effect of dipyridamole on the incidence of clinically detectable deep vein thrombosis. Lancet ii:718-721, 1969
23. O'Brien JR, Tulevski V, Etherington M: Two in vivo studies comparing high and low aspirin dosage. Lancet i:399-400, 1971
24. Salzman EW, Harris WH, DeSanctis RW: Reduction in venous thromboembolism by agents affecting platelet function. N Engl J Med 284:1287-1292, 1971
25. Sharnoff JG: Results in the prophylaxis of postoperative thromboembolism. Surg Gynec Obstet 123:303-307, 1966
26. Kakkar VV, Nicolaides AN, Field ES, et al: Low doses of heparin in prevention of deep-vein thrombosis. Lancet ii:669-671, 1971
27. Nicolaides AN, Desai S, Douglas JN, et al: Small doses of subcutaneous sodium heparin in preventing deep venous thrombosis after major surgery. Lancet ii:890-893, 1972
28. Kakkar VV, Spindler J, Flute PT, et al: Efficacy of low doses of heparin in prevention of deep-vein thrombosis after major surgery. Lancet ii:101-106, 1972
29. Gordon-Smith IC, Le Quesne LP, Grundy DJ, et al: Controlled trial of two regimens of subcutaneous heparin in prevention of postoperative deep-vein thrombosis. Lancet i:1133-1135, 1972
30. Gallus AS, Hirsh J, Tuttle RJ, et al: Small subcutaneous doses of heparin in prevention of venous thrombosis. N Engl J Med 288:545-551, 1973
31. Wessler S, Yin ET, Butler JV: A sensitive quantitative assay for heparin in biological fluids. Circulation 44, Suppl II 79, 1971
32. Handley AJ: Low-dose heparin after myocardial infarction. Lancet ii:623-624, 1972
33. Wray R, Maurer B, Shillingford J: Prophylactic anticoagulant therapy in the prevention of calf-vein thrombosis after myocardial infarction. N Engl J Med 288:815-817, 1973
34. Yin ET, Wessler S, Stoll PJ: Biological properties of the naturally occurring plasma inhibitor to activated Factor X. J Biol Chem 246:3703-3711, 1971
35. Wessler S, Yin ET: Theory and practice of minidose heparin in surgical patients. Circulation XLVII:671-676, 1973
36. Barritt DW, Jordon SC: Anticoagulant drugs in treatment of pulmonary embolism: Controlled trial. Lancet i:1309-1312, 1960
37. Basu D, Gallus A, Hirsh J, et al: Monitoring heparin treatment with activated partial thromboplastin time. N Engl J Med 287:324-327, 1972
38. Mavor GE, Walker MG, Dhall DP: Peripheral venous scanning with ^{125}I-tagged fibrinogen. Lancet i:661-663, 1972

Refer to: Hemophilia and von Willebrand's disease—Fourth Annual Paul M. Aggeler Memorial Lecture—Medical Staff Conference, University of California, San Francisco. West J Med 120:226-232, Mar 1974

Hemophilia and von Willebrand's Disease

Fourth Annual Paul M. Aggeler Memorial Lecture

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. WILLIAMS:* *Today's Medical Grand Rounds at the San Francisco General Hospital represents the fourth annual Paul M. Aggeler Memorial Lecture. I will call upon Dr. Wallerstein to introduce our distinguished guest.*

DR. WALLERSTEIN:† He is Dr. Oscar D. Ratnoff. His professional life has been associated in the main with three medical institutions, Columbia, Johns Hopkins and Case Western Reserve. He has been at Case Western Reserve since 1950 and is Professor of Medicine there. He is a Career Investigator of the American Heart Association and is a member of numerous professional organizations. These include the American Society for Clinical Investigation, the Association of American Physicians and the American Society of Hematology of which he is vice-president. He is the author of about 200 publications. Several of these are landmarks in their fields, such as his review of cirrhosis with Patek in 1942, one of the first papers on disseminated intravascular coagulation in 1954, and the first description of the Hageman factor in 1955. His work on circulating anticoagulants, psychogenic purpura, complement, and antihemophilic factor-like antigens is well respected and provides the subject of his remarks today.

DR. RATNOFF:‡ Thank you, Dr. Wallerstein. The opportunity to give this fourth Paul Aggeler Memorial Lecture has special meaning for me. Paul Aggeler was a close friend whose perceptive mind and gentle personality provided me with a companionship which I cherished. His interests covered the broad scope of our peculiar specialty, and throughout his career he made numerous major contributions.

I first became acquainted with Paul vicariously, through a small volume which he wrote with Dr. Salvatore Lucia entitled *Hemorrhagic Disorders: A Guide to Diagnosis and Treatment.* It is a model primer of hemorrhagic disease, and its clinical descriptions are still valid and vivid after more than a quarter of a century. Among its many illustrations is the painting of a boy with

*Hibbard Williams, MD, Vice Chairman and Professor of Medicine.

†Ralph O. Wallerstein, MD, Clinical Professor of Medicine and Clinical Pathology, and Lecturer in Medicine, San Francisco General Hospital.

‡Oscar D. Ratnoff, MD, Professor of Medicine, Case Western Reserve University School of Medicine and Career Investigator of the American Heart Association.

severe hemophilia. It serves as an appropriate introduction to what I shall have to say this morning.

As we grow older, we become painfully aware that each of the subjects we learned in our youth has become infinitely more complex. The complexities are the natural result of the discovery of new information which has to be correlated with our earlier knowledge, so that we must always revise the way we look at things. Terrifying as this burden may appear, the complexities often help us to understand puzzles that have mystified us before. Thus in a paradoxical way they act to simplify our understanding. I would like to review some of our current comprehensions of two closely related disorders, classic hemophilia and von Willebrand's disease. In recent years our understanding of these two diseases has become much more complex. But these complexities have led us to simpler ways of diagnosing these disorders and caring for patients afflicted with them.

I have always wondered why such rare disorders as hemophilia and von Willebrand's disease have been the subject of so much research endeavor. On one level, perhaps this reflects our primitive fears of bleeding; every little child runs to his mother in panic at the sight of a tiny scratch. On another level, perhaps our fascination with hemorrhagic disorders stems from our excitement at seeing clinical observation translated to laboratory investigation, and information gathered in the laboratory translated back to the care of the patient. Certainly, the implications of the phrase "the experiments of nature" are exemplified in the clearest way by the hereditary disorders of blood coagulation.

That certain hemorrhagic disorders run in families is a very old observation. In the sixth century A.D., one Rabbi Ben Gamilieal exempted from circumcision a boy whose brothers had bled after this procedure. Much more recently, early in the nineteenth century, a New York physician, Otto, described families in which a severe bleeding tendency was confined to males but appeared to be transmitted by women. Long before chromosomes were discovered, then, Otto had discerned that hemophilia was transmitted as a sex-linked characteristic.

Our present conception of the pathogenesis of bleeding in hemophilia derives from the studies of Wright at the end of the last century. He demonstrated that the blood of affected persons clotted abnormally slowly. Some years later, Thomas Addis of Stanford University pointed out that patients with hemophilia were unable to form thrombin at a normal rate. Still later, in the mid-1930's, Patek and Stetson separated a globulin fraction of normal plasma that shortened the clotting time of hemophilic blood. By contrast, the corresponding fraction of hemophilic plasma lacked this property. The agent in normal plasma is now usually referred to as antihemophilic factor or Factor VIII.

Patek's observations found almost immediate application in therapy. Plasma or fractions of plasma rich in antihemophilic factor have come into use to correct temporarily the hemophiliac's clotting defect and to control bleeding. Therapy with plasma alone was often inadequate because the quantities needed for hemostasis taxed the circulation. Fortunately, within the last few years several excellent ways of preparing fractions of plasma rich in antihemophilic factor have become available. In general, two types of preparation are used clinically.

We owe the first type, cryoprecipitated antihemophilic factor, to Dr. Judith Pool and Dr. Edward Hershgold of Stanford. In this technique antihemophilic factor is separated from fresh plasma because it is insoluble at low temperatures. Once the cryoprecipitate has been separated, the rest of the plasma can be restored to the blood cells for use in transfusions of whole blood. The cryoprecipitate itself is stored in the frozen condition until needed.

The second type of preparation is lyophilized, allowing greater flexibility in use. The material which is lyophilized is either cryoprecipitated antihemophilic factor or antihemophilic factor which has been precipitated from plasma by the addition of neutral amino acids. Nothing comes without cost. The advantage of the lyophilized preparations must be balanced against the increased risk that hepatitis will develop in the recipient, since literally thousands of blood donors provide the plasma for each batch.

The availability of concentrates of antihemophilic factor has allowed us to tide most patients over acute episodes of bleeding, and to subject them to surgical procedures which we would not have dreamed of permitting even ten years ago. Moreover, it has increased the mobility of pa-

tients with hemophilia, who can now undertake trips away from home by carrying with them lyophilized preparations. It also has made home treatment of hemophilia feasible when bringing the patient to the hospital for transfusion would impose a major handicap to good care.

In 1953, Paul Aggeler demonstrated that patients who by all clinical criteria seemed to have hemophilia could be divided into two groups. The first, said to have classic hemophilia, were deficient in Patek's antihemophilic factor. Those in the second group lacked an entirely different clot-promoting agent, called plasma thromboplastin component or PTC by Dr. Aggeler and Christmas factor or Factor IX by others. Their disorder, Christmas disease, is only about one-tenth as common as classic hemophilia. As transfusion therapy developed, it became of great importance to distinguish classic hemophilia from Christmas disease, since preparations rich in antihemophilic factor are without benefit in the treatment of Christmas disease. The need for replacement therapy in such patients has been met by the use of concentrates of factor IX, a field to which Dr. Aggeler made major contributions.

Almost as soon as Patek reported that hemophilia was associated with a functional deficiency of antihemophilic factor, a new complexity appeared. Some patients who had been treated with plasma or fractions of plasma rich in antihemophilic factor became refractory to further transfusion therapy. The plasma of these patients was found to contain agents with the peculiar property of inactivating antihemophilic factor, so that therapy with this agent was ineffective. The destruction of antihemophilic factor is apparently due to the presence in the patient's plasma of antibodies (usually called circulating anticoagulants) directed against antihemophilic factor, to which the patients have been sensitized by treatment. Why only certain patients suffer this complication is unknown. Many attempts have been made to treat these patients with immunosuppressive agents. Although an occasional patient seems to benefit from such measures, nearly all are refractory even to heroic attempts to suppress antibody formation. Unfortunately, the appearance of these circulating anticoagulants is a relatively common event. At least one-fifth of my patients with severe classic hemophilia have this complication, making their care exceedingly difficult.

As knowledge concerning the clotting process increased, techniques were developed to assess the concentration of antihemophilic factor, as measured in functional tests, with reasonable accuracy. From these tests it was learned that the concentration of antihemophilic factor varied remarkably in normal persons, and was increased after exercise, during stress, in pregnancy and in certain pathological states. Further, the concentration of antihemophilic factor in these functional tests varied in different patients with hemophilia, a variation paralleling the clinical severity of the disease.

The capacity to measure antihemophilic factor had an unexpected result. Some years ago, von Willebrand described a bleeding disorder among the inhabitants of the Åland Islands, which are located off the coast of Finland. Unlike hemophilia, this disease affected both men and women and was inherited as a dominant trait. Also unlike hemophilia, in which the severity of the disease is pretty much the same in all affected members of a given family, the intensity of the bleeding tendency in von Willebrand's disease varies from person to person within a family. Another feature which aroused great interest was that the bleeding time (that is, the time elapsing until bleeding from a deliberately inflicted wound stops) is prolonged. In contrast, the bleeding time is normal in classic hemophilia.

When it became possible to measure antihemophilic factor in the early 1950's, it was soon found that a second abnormality is usually present in patients with von Willebrand's disease. This is a deficiency of antihemophilic factor. Von Willebrand's disease has other noteworthy features. When either normal or hemophilic blood is filtered through a column of glass beads, a large proportion of its platelets are retained by the glass filter. In contrast, in most patients with von Willebrand's disease, adhesion of platelets to the filter is impaired. A rough correlation exists between the degree to which the bleeding time is prolonged and the degree to which the retention of platelets by the glass filter is impaired. A second abnormality of platelets has been described recently by Howard and Firkin in Australia. When the antibiotic ristocetin is added to platelet-rich normal plasma, the platelets clump. The same phenomenon is seen with platelet-rich hemophilic plasma. But ristocetin does not clump the platelets of patients with von Willebrand's disease.

Another interesting aspect of von Willebrand's

disease is the response of patients to transfusion. When patients with classic hemophilia are transfused with preparations containing antihemophilic factor the concentration of this substance, as measured in clotting assays, rises immediately to the predicted value. Thereafter its titer falls rapidly so that after 10 to 12 hours only half of the amount infused is still detectable.

The situation in von Willebrand's disease is dramatically different. When patients with von Willebrand's disease are transfused with normal plasma, the titer of functional antihemophilic factor rises immediately to the predicted level. But then the titer increases still further during the next 6 to 8 hours, and thereafter falls much more slowly than in classic hemophilia. Still more remarkably, the same rise and fall follows the transfusion of hemophilic plasma. Thus in von Willebrand's disease the transfusion of plasma deficient in antihemophilic factor, as measured in clotting assays, induces the appearance of an agent with the functional characteristics of antihemophilic factor. The transfusion of normal or hemophilic plasma also corrects the prolonged bleeding time of patients with von Willebrand's disease, but the effect is transient. Twenty-four hours after transfusion, at a time when the concentration of antihemophilic factor is still elevated, the bleeding time is again abnormally long.

I began my remarks with the thesis that as time passes, the subjects we learned in our youth become infinitely more complex, but that the complexities often help us to solve puzzles that had eluded us before. For many years, the natural assumption was drawn that the plasma of patients with hemophilia was deficient in antihemophilic factor. A contrary view, to which little attention was paid, was expressed by Shanberge and Gore in 1957. They presented evidence that, in opposition to the general belief, the plasma of patients with hemophilia indeed contained antihemophilic factor, but that this substance was in an abnormal form which would not promote the clotting process. This intriguing concept did not gain acceptance, largely because it proved difficult to confirm the experimental observations.

Early in 1970, working with Dr. Theodore Zimmerman and Dr. Arnold Powell, we prepared highly purified antihemophilic factor by methods suggested by Dr. Hershgold and others. We used this purified material to prepare a potent antiserum in rabbits, and with this specific antiserum we were able to confirm the observation of Shanberge and Gore. Our antiserum inhibited the clotting of normal plasma because it inactivated antihemophilic factor. We could block the action of the antiserum by adsorbing it with normal plasma that contains antihemophilic factor, the antigen against which the antiserum was directed. But we were also able to block the antiserum with hemophilic plasma. Presumably, then, hemophilic plasma did contain material which was antigenically related to antihemophilic factor.

This neutralization technique is very cumbersome. We therefore took advantage of another property of our antiserum; it formed a precipitate when it was mixed with its antigen, antihemophilic factor. We turned to a conventional form of immunologic assay, that is, Laurell's technique of semi-quantitative immunoelectrophoresis. Rabbit antiserum to antihemophilic factor was imbedded with agarose into a gel formed on a glass plate. A series of holes was then cut into one end of the gel, and the plasmas to be tested were placed within these wells. A current was then applied across the plate. After a while precipitin lines formed, the heights of which were a function of the concentration of antigenic material in plasma related to antihemophilic factor. No longer unexpectedly, hemophilic plasma, measured by this technique, contained at least as much antigen as normal plasma. By contrast, the plasma of patients with von Willebrand's disease contained antigenic material in rough proportion to the concentration of functional antihemophilic factor.

Thus, classic hemophilia appears to be a disorder in which the concentration of functional antihemophilic factor is reduced, while that of antigenic material related to antihemophilic factor is normal. In contrast, von Willebrand's disease appears to be associated with a deficiency of both functional and antigenic antihemophilic factor—that is, patients with this disorder have a true deficiency of antihemophilic factor. These results have been present in all of 58 patients with classic hemophilia and in 34 patients with von Willebrand's disease.

Dr. Stites, here in San Francisco, obtained essentially the same results that I have described, using the technique of tanned red cell hemagglutination inhibition. I cannot refrain from mentioning that Dr. Lawrence Kass and I used this same technique and obtained similar results in 1968, but we did not publish the data since we

were unprepared to depart from the ruling dogma that hemophilia was due to a deficiency of antihemophilic factor. It took us two years to convince ourselves that the ideas of our youth were wrong.

Now we had the tools to re-examine the effects of transfusion in hemophilia and von Willebrand's disease. Three patients with classic hemophilia were transfused with a single bolus of cryoprecipitated antihemophilic factor, all in the treatment of an episode of hemarthrosis. Measured in clotting tests, the infused antihemophilic factor disappeared rapidly, which is the anticipated result. By contrast, the concentration of antigens to antihemophilic factor disappeared much more slowly.

Among possible explanations for this dissociation, two are of particular interest. Perhaps the antigens we studied are not really related to antihemophilic factor at all. Alternatively, cryoprecipitates may contain two forms of antihemophilic factor, one of which functions in clotting and the other is inactive. The first is rapidly cleared from the circulation, while the second lingers for a longer time. Studies of cryoprecipitates prepared by Dr. Bruce Bennett and me, using Pool's method, have indeed demonstrated that there are two populations of antihemophilic factor in these materials, and that only one has functional activity.

An entirely different result was found in von Willebrand's disease. When a patient with this disorder was transfused, the anticipated rise in functional antihemophilic factor during the hours after transfusion took place, and the subsequent fall in titer was much slower than that in classic hemophilia. At the same time, however, the concentration of antigens related to antihemophilic factor fell rapidly after transfusion, reaching preinfusion levels within a day.

Again we are faced with several possibilities. Perhaps the antigenic material is not really related to antihemophilic factor. Were this the case, it would be difficult to explain why the antigenic material disappears from plasma at different rates in hemophilia and von Willebrand's disease. Alternatively, the antigenic material could be a mixture of functional and non-functional antihemophilic factor. Were this so, the non-functional material could induce the formation of functional antihemophilic factor in the patient with von Willebrand's disease. One possible implication of this view is that the material in these patients may be antigenically distinct from normal antihemophilic factor.

Some further clues are available. One striking feature of von Willebrand's disease, you will recall, is that the retention of platelets to columns of glass beads is impaired. Bouma, in the Netherlands, found that he could correct the defect in platelet retention by mixing the blood of patients with von Willebrand's disease with purified antihemophilic factor. He could achieve the same result by mixing the patient's blood with the corresponding fraction of hemophilic plasma which contains the antigenic material. Thus, the defect in platelet retention seems to be related to the deficiency in antihemophilic factor-like material. This observation has been repeated in various ways and appears to be correct. You will recall, too, that the aggregation of platelets by ristocetin is impaired in von Willebrand's disease, but not in hemophilia. Weiss, in New York, and others have now demonstrated that the defect in aggregation of platelets by ristocetin can be corrected by adding purified antihemophilic factor to the plasma of a patient with von Willebrand's disease.

I mentioned earlier that the prolonged bleeding time of patients with von Willebrand's disease is shortened by the transfusion of normal plasma, but that this effect lasts for only a few hours. The temptation is great to ascribe the shortening of the bleeding time to the transfusion of antigenic material related to antihemophilic factor. We have had the chance to test this in three patients with von Willebrand's disease. Under stress, the concentration of functional activity rose to normal in these patients. At the same time, the concentration of antigenic material related to antihemophilic factor also reached normal levels. But the bleeding time remained longer than 15 minutes. In other words, the presence of normal amounts of antigenic material did not correct the bleeding time. One must not attempt to draw too firm a conclusion from these observations. Perhaps in von Willebrand's disease, the antigenic material is *qualitatively* different from that in normal plasma.

This and similar experiments have had an unexpected result. Some critics of our studies have proposed that the antigenic material in hemophilic plasma is not related to antihemophilic factor at

all, a possibility I mentioned earlier. Several types of observation make this seem unlikely. As I pointed out, in pregnancy, during various stresses and in hepatic cirrhosis, the concentration of antihemophilic factor rises, sometimes to dramatically high levels. This rise in titer is paralleled by a corresponding rise in the concentration of antigens related to antihemophilic factor. Presumably, then, whatever induces the rise in functional antihemophilic factor also induces a rise in antigenic material, suggesting that they may be related.

We have examined the problem in other ways. For example, we prepared antiserum to the nonfunctional antigenic material in hemophilic plasma. This antiserum detected apparently identical antigens in normal and hemophilic plasma, but not in von Willebrand's plasma. More strikingly, the antiserum readily inactivated the antihemophilic factor in normal plasma, demonstrating that it was directed against this specific protein. Moreover, fractions prepared from normal and hemophilic plasmas had the same sedimentation behavior upon ultracentrifugation and the same subcomponents after fragmentation. In other words, the plasma of a hemophiliac contains material which is closely similar to normal antihemophilic factor.

A major problem in the care of hemophiliacs is detection of the carrier state in the female relatives of these patients. You will recall that each somatic cell of males contains an X and a Y chromosome, while that of females contains two X chromosomes. A carrier female has one abnormal X chromosome and one normal X chromosome. Following the rules of chance, half her sons will inherit the abnormal X chromosome and will be hemophiliacs, while half her daughters will be carriers. In the next generation, all the daughters of a hemophiliac inherit the abnormal X chromosome and are obligate carriers, while his sons are always normal and cannot transmit the disease.

We can be certain that the daughters of a patient are carriers and that the mother of two hemophilic sons is a carrier. We can be equally certain that the mother of a hemophiliac is a carrier if she has other affected relatives. But we cannot predict which of a carrier's daughters are themselves carriers; such women have an even chance of being carriers or being normal.

For many years, the only way we could detect the carrier state was to measure antihemophilic activity in clotting assays. Modern genetic theory tells us that, in females, only one of the two X chromosomes in each somatic cell is functional. How this comes about is not clear, but at an early stage of embryonal development one of the X chromosomes in each somatic cell becomes inactive. Which X chromosome is functional in any given cell is a matter of chance. After this election has been held, the same X chromosome remains active in all descendants of the cell. Hemophilic carriers have one normal and one abnormal X chromosome, one from each parent. Thus, on the average, carriers should have half the normal number of *functional* X chromosomes that are capable of directing the synthesis of normal antihemophilic factor. Carriers, then, should synthesize half the normal amount of functional antihemophilic factor.

In fact, when one measures functional antihemophilic factor in carriers, the average titer is just about one-half that of normal persons. But the wide scatter of titers among both normal women and carriers is such that only about one-fourth of carriers can be identified by clotting assays alone.

A solution to the problem of identifying carriers can be derived from the observation that all hemophiliacs synthesize normal amounts of antigenic material related to antihemophilic factor. Presumably then, in a carrier one X chromosome directs the synthesis of normal antihemophilic factor, while the other X chromosome directs the synthesis of the abnormal, non-functional antigenic material. By measuring both functional and antigenic antihemophilic factor, we should be able to detect the carrier state with a high degree of certainty. One would anticipate that in carriers, regardless of the concentration of functional antihemophilic factor, the concentration of antigenic material should be relatively high. Using this criterion, we have now tested 51 certain carriers; we have been able to detect the carrier state in 96 percent of them with a degree of confidence of greater than 99 percent.

If our assumptions are correct, we should anticipate that we should be able to detect the carrier state in half the daughters of carriers if these daughters have not had sons, since these women have an even chance of being carriers. We have now tested 41 such potential carriers, none of

whom had a son. Nineteen, or 46 percent, have proved to be carriers in our test.

We have devised an even more severe test of our method. Genetic theory tells us that if the daughter of a carrier has had one normal son, she still has a 33 percent chance of being a carrier. We have now examined seven daughters of carriers who have had one normal son. Two of these (or 29 percent) have the laboratory characteristics of carriers, while five seem normal by our technique.

Sometimes we are approached by the mother of a patient with hemophilia who has no other known relatives with this disease. Of course she is anxious to learn whether she is a carrier, or whether the disease has been the result of some mutation in the ovum from which her child arose —although she will not put it in this arcane language. We have now tested 25 such mothers of sons with sporadic hemophilia. Eighteen of these mothers have proved positive in our tests—that is, unbeknownst to them, they were in fact carriers. The test was negative in the other seven patients. Perhaps, in some of these seven, the disease indeed resulted from mutation of the ovum from which the hemophiliac arose.

Finally, a glimpse of the future. Antihemophilic factor, as separated from plasma, is a giant molecule. Studies from several laboratories, including our own, have demonstrated that this molecule can be broken up into sub-units by reduction, presumably through disruption of S-S bonds. The predominant species of sub-unit has a molecular weight of about 200,000. Moreover, as was probably first shown by Weiss, a functional sub-unit of antihemophilic factor still possessing clotting activity can be separated from antihemophilic factor by increasing the ionic strength dramatically. It is tempting to believe that this sub-unit is held to the rest of the molecule by weak, noncovalent bonds, such as hydrogen bonds. It is not beyond possibility that this fragment can be analyzed and perhaps synthesized. Were this the case, both prophylaxis and therapy of hemophilia would be greatly simplified.

I have tried to demonstrate by example that the growing complexity of our knowledge may, in fact, result in simplifying explanations for natural phenomena. I have shown that the patient with von Willebrand's disease appears to be truly deficient in both functional and antigenic antihemophilic factor. By contrast, the patient with classic hemophilia deficient in functional antihemophilic factor has within his plasma normal amounts of antigenic material related to this substance. Knowledge of these facts has enabled us to detect the carrier state in a high proportion of known conductors of hemophilia. What started as complexity turns out to have systematized and simplified our understanding of these two diseases. I regret that Paul Aggeler is not here to participate in these new ventures. He would have enjoyed the unravelling of mysteries that were very much a part of his life.

Important Advances in Clinical Medicine

Epitomes of Progress—Ophthalmology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Ophthalmology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Ophthalmology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Ophthalmology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities
California Medical Association, 731 Market St., San Francisco, CA 94103

Ocular Tumor Diagnosis

B-SCAN ULTRASONOGRAPHY has added a new dimension to the diagnosis of intraocular tumors. When coupled with A-scan ultrasound studies it is a highly reliable method of detecting solid growths within the globe. It has its greatest value for eyes with opaque media.

The B-scan produces a two-dimensional outline of the eyeball and the intraocular structures, giving the effect of a silhouette on the monitoring oscilloscope. This affords the examiner a highly desirable over-all perspective. The B-scan unit is hand-operated and allows the scan to be frozen at any position of the monitored display for photographing or study. The echoes show as bright dots on the screen as contrasted to the wave pattern on the A-scan ultrasonoscope.

In B-scan echograms a malignant melanoma appears as a convex surface. Due to the homogeneity of the tumor, acoustic shadowing indicates an acoustically hollow area in the mass. In such cases the A-scan radiofrequency echo reveals the solid nature of the growth. An additional B-scan feature of a melanoma is the angular outline often seen at the inner apex of the echo. Tumor masses of 1 mm thickness have been discovered. The detection on the sonogram of a serious detachment associated with the solid choroidal mass adds confirmatory diagnostic evidence.

In a series of 18 intraocular tumors Coleman reported there were no false-negatives. In his total experience only one melanoma was missed, and he has yet to report a false-positive. This emphasizes the reliability of the method under ideal conditions.

Chronologic ultrasonic studies in addition to fundus photography and fluorescein angiography are of great value in differential diagnosis when intraocular tumor is suspected and observation over a considerable period is necessary. An additional use of ultrasound in cases of ocular tumors is to determine the size of the tumor so that the proper choice of the size and radioactivity of an implant can be made. The regression of the tumor can also be followed.

However, this method is not as reliable for

diagnosing angiomas because they can be confused with an inflammatory or serous retinal elevation. Retinoblastomas of less than 2 mm are easily missed unless they contain calcium deposits which are highly reflective to the ultrasonic vibrations.

In Coleman's opinion, ultrasound is the best "non-invasive" test for intraocular tumors available.

GEORGE L. TABOR, MD

REFERENCES

Coleman DJ, Konig WF, Katz L: A hand-operated ultrasound scan system for ophthalmic evaluation. Am J Ophthalmol 68: 256-263, Aug 1969

Coleman DJ: Reliability of ocular and orbital diagnosis with B-scan ultrasound. I. Ocular diagnosis. Am J Ophthalmol 73: 501-516, Apr 1972

Keeney A: Personal communication. Nov 1972

B-Scan of Normal Eye (15MHz). Note pupillary aperture (P), passage of the optic nerve through retrobulbar fat (ON) and normal ocular contour.

Ultrasonography in Ophthalmology

ULTRASONOGRAPHY HAS BECOME an important diagnostic technique in ophthalmology, particularly during the past few years. The development of high resolution instruments has made it possible to examine the eye and orbit carefully with both the A-scan (time-amplitude) and the B-scan (scanned, intensity-modulated) techniques. Each of these techniques has certain advantages. Examination with the A-scan is somewhat more rapid and a careful examination of the globe can be made by using quantitation and kinetic studies. Through tissue calibration, an actual differentiation of intraocular and orbital lesions often can be diagnosed. B-scan ultrasonography has the advantage of giving an anatomical display very similar to that of a section through the eye and orbit, and this facilitates the interpretation.

Ultrasonography provides a means for examining eyes that cannot be visualized because of corneal opacities, cataracts, hemorrhages and the like. In this way retinal detachments, tumors, hemorrhages, and foreign bodies can be diagnosed and evaluated. These techniques are particularly applicable in cases of exophthalmos, as the other forms of orbital study often do not provide adequate information for making a diagnosis.

J. WILLIAM KOHL, MD

REFERENCES

Coleman DJ: Reliability of ocular and orbital diagnosis with B-scan ultrasound. Am J Ophthalmol 73:501-516 Apr 1972

Ossoinig K: Ultrasonic diagnosis on the eye: An aid for the clinic (Review). Ultrasonics in Ophthalmology Symposium, Münster, Germany Aug 1966, pp 116-133, Basel/New York, Karger Co, 1967

Cosmetic Operations on the Eyelids

BLEPHAROPLASTY is a frequently performed operation in which excess tissue is removed from the eyelids. Removal of too little tissue can be remedied by reoperation. Removal of too much tissue can be disastrous. To help avoid overexcision, skin clamps have been designed which can be placed on the skin, removed, and reapplied until the excess is accurately determined.

A new method for marking the skin before removal also has been developed. Tissues are injected with a local anesthetic agent to which hyaluronidase has been added. After 30 minutes the skin can be pinched and the undersurfaces will seem to adhere. The "roll" of skin to be excised can be adjusted to the proper amount before any incision is made. Excision is quickly done with scissors. The use of this "pinch" technique has proven quite effective.

A new operation to provide dynamic closure of the lids affected by facial paralysis has been devised. It consists of threading a fine silicone rubber rod along the pretarsal areas of both upper and lower lids, and securing it at the canthi. The levator then can open the eye, and when the levator relaxes, a sphincter-like action closes the lids. The operation also helps to elevate the sagging lower lid and reduces the epiphora. The rod must be carefully inserted under just the right tension. There may be complications such as infection, extrusion, entropian and ectropion. However, this technique seems superior to the use of gold

weights, wire springs, and temporal muscle transplants. It is considered a distinct advance in the surgical treatment of facial paralysis.

CROWELL BEARD, MD

REFERENCES

Feldstein M: Skin clamps in cosmetic blepharoplasty. Arch Ophthal 88:659 1972

Parkes M, Fein W, Brennan HG: Pinch technique for repair of cosmetic eyelid deformities. Arch Ophthalmol 89:324 1973

Arion HG: Dynamic closure of the lids in paralysis of the orbicularis muscle. Int Surg 57:48-50, Jan 1972

Operations on the Vitreous Body

UNTIL RECENTLY, surgical manipulation of the vitreous body has been avoided, but technical advances now have made new intraocular procedures possible. These include vitreous removal and vitreous membrane resection. Hence some patients with previously untreatable diseases causing vitreous opacification can now be helped. These conditions include longstanding vitreous hemorrhage (from diabetic retinopathy, trauma, bleeding disorders, hypertensive retinopathy and the like), ocular inflammatory diseases, and metabolic diseases such as primary amyloidosis. Removal of the opacified vitreous humor clears the pathway for light through the eye. If the retina is intact and the other ocular media are clear, visual function can be substantially improved.

Vitreous membrane resection has been helpful in some of the complicated forms of retinal detachment and in the management of some of the vitreous complications of cataract operations. The tractional phenomena, which are the most important aspects, can often be ameliorated by cutting and resecting the vitreous membranes or bands.

ALLAN E. KRIEGER, MD

REFERENCES

Straatsma BR, Foos RY, Kasner D, et al: Symposium: Surgery of the vitreous body. Trans Am Acad Ophthalmol Otolaryngol 77:168, 1973

Machemer R, Parel JM, Norton EWD: Vitrectomy: A pars plana approach—Technical improvements and further results. Trans Am Acad Ophthalmol Otolaryngol 76:462, 1972

Optic Disc Vasculitis—A Benign but Prolonged Form of Disc Edema

A MONOCULAR condition variously called retinal vasculitis, papillophlebitis and papillary vasculitis occurs in otherwise healthy young adults. Although ophthalmoscopically it is indistinguishable from papilledema or papillitis, the intracranial pressure is normal, and vision is little affected. Extensive neurosurgical investigations have always been normal.

The chief symptoms are vague, intermittent, evanescent (minutes to hours) scotomata, often on awakening. Visual acuity is usually better than 20/30. No Marcus Gunn pupillary sign is present, and color vision is normal. Enlargement of the blind spot is the only perimetric finding. The ocular signs are confined to the posterior pole: Severe disc edema, peripapillary cotton wool spots, and dilated and tortuous veins with perivenous hemorrhages. Elevation of retinal venous pressure with normal arterial pressures (systolic and diastolic) is seen on ophthalmodynamometric examination. Delay in arterial and venous filling with leakage of dye from the disc and larger veins is noted on fluorescein angiography. Later, decompensation of the perimacular capillary bed may be seen.

Though the final visual results are almost always good, the fundus changes may take six to eighteen months to clear, leaving perivenous sheathing and dilated venules on the disc's surface as sequelae. Treatment with acetazolamide, anticoagulants, or steroids has not affected the course of this condition.

The cause is thought to be occlusion of the retinal veins, in the absence of arterial disease. This occlusion is possibly precipitated by phlebitis of the perioptic veins. The underlying cause of the vasculitis is unknown.

RICHARD L. SOGG, MD

REFERENCES

Hart CD, Sanders MD, Miller SJH: Benign retinal vasculitis: A clinical and fluorescein angiographic study. Br J Ophthalmol 55: 721, 1971

Editorial: Optic-disc vasculitis. Lancet 2:1186-1187, Dec 2, 1972

Hayreh SS: Optic disc vasculitis. Br J Ophthalmol 56:652-670, Sep 1972

Electromyography

DURING the past 20 years, there has been great interest in ocular electromyography (EMG) by various investigators including Breinin, Jampolsky, Blodi, Huber and Scott. Jampolsky recently concluded that electromyography is not useful in the management of the usual strabismus patient, although it may be helpful to an understanding of strabismus mechanisms and in cases of frank neurologic disease. Clinically useful information can be obtained in Duane's syndrome, thyroid disease, myasthenia gravis and some of the myopathic conditions. For example, in Duane's syndrome, normal medial rectus function accompanied by abnormal lateral rectus innervation is always found. Studies involving the use of an EMG needle with multiple electrodes placed at different sites along its shaft promise to yield interesting

information concerning the activity of different fibers within an extraocular muscle. This should provide a physiologic correlate for the role of various muscle fiber types in the control of ocular position and movement (fixation, saccades, versions and vergences).

HENRY S. METZ, MD

REFERENCES

Jampolsky A: What can electromyography do for the ophthalmologist? Invest Ophthalmol 9:570-599, 1970

Scott AB, Wong GY: Duane's syndrome. An electromyographic study. Arch Ophthalmol 87:140-147, Feb 1972

Management of Tear Duct Disease

EPIPHORA is an extremely annoying problem to persons of all ages. Approximately 5 percent of infants are born with one or both tear ducts blocked. In about half of these cases, the ducts will open as the child grows. When this does not happen, gentle probing through the nasal lacrimal duct into the nose will cure the vast majority of patients, although sometimes the procedure has to be repeated. It can be performed in the physician's office, but is safer if performed under anesthesia so that a false passage is not made inadvertently.

In adults the cause of epiphora must be ascertained, if possible. This is particularly important in patients with allergic disease, especially those with allergic conjunctivitis who often have persistent or intermittent tearing. The condition usually can be controlled with topical antiallergic medication. Tearing associated with infectious disease is also annoying, but generally responds to local antibiotic therapy. Mechanical obstruction of the nasolacrimal system ordinarily has to be relieved by some form of surgical procedure.

If the gentle introduction of a probe into the punctum and through the nasal lacrimal duct shows the system is patent as far as the nose and cannot be opened by the instillation of drugs, such as procaine or cocaine, then operation must be considered. There are many variations of the classical dacryocystorhinostomy procedure. In the hands of a competent surgeon, most of the techniques work. If the lower canaliculus is blocked and the upper one is open, many patients, especially older ones, can manage without too much discomfort. In younger people, particularly those interested in sports, wind may cause excessive tearing. In such cases when one or both canaliculi are blocked, the procedure of choice is the Jones operation of the conjunctivo-dacryocystorhinostomy. In these cases a pyrex tube is placed so that it extends from the conjunctival sac into the lacrimal sac with an adequate opening into the nose. There have been several modifications of this procedure, but the classical one is undoubtedly still the best. Other materials such as silicone have been substituted for pyrex, but glass absorbs water and most plastic materials repel it.

Less common causes of epiphora must always be considered. Occasionally there is a tumor of the tear sac. Dacryoadenitis is rare, whether inflammatory or due to a neoplasm. Surgical operation or radiation, or both, may be indicated in treatment of tumors located in the lacrimal system.

WARREN A. WILSON, MD

REFERENCES

Chanler PA: Dacryocystorhinostomy. Trans Am Ophthalmol Soc 34:240, 1936

Mustarde JC, Jones LT, Callahan A: Ophthalmic Plastic Surgery Up to Date. Aesculapius, Birmingham, 1970

Wadsworth JAC, Chandler AC Jr: A modified conjunctivo-dacryocystorhinostomy. Trans Am Ophthalmol Soc In press

Ryan SJ, Font RL: Primary epithelial neoplasms of the lacrimal sac. Am J Ophthalmol 76:73 1973

ADVISORY PANEL TO THE SECTION ON OPHTHALMOLOGY

GEORGE K. KAMBARA, MD, *Chairman, Los Angeles*
RUSH BLODGET, JR, MD, *Vice-Chairman, Redding*

JOHN BERG, MD
CMA Section on Ophthalmology
Chairman
Sacramento

ROBERT CHRISTENSEN, MD
CMA Section on Ophthalmology
Secretary
Los Angeles

JERRY DONIN, MD
CMA Section on Ophthalmology
Assistant Secretary
Pomona

BRADLEY STRAATSMA, MD
CMA Scientific Board
Los Angeles

BYRON DEMOREST, MD
Sacramento

THEODORE STEINBERG, MD
Fresno

ROBERT V. SHEARER, MD
Loma Linda University

A. RALPH ROSENTHAL, MD
Stanford University

GERALD PORTNEY, MD
University of California, Davis

JOSEPH TIRICO, MD
University of California, Irvine
California College of Medicine

GEORGE TABOR, JR, MD
University of California, San Diego

MICHAEL J. HOGAN, MD
University of California, San Francisco

WARREN A. WILSON, MD
University of Southern California
Los Angeles

EDITORIAL

Are Carrots and Sticks for Donkeys, or for Doctors?

For more than a decade, health care has been advertised as a national crisis although the public seems to put it pretty far down the list of national problems. Be that as it may, Congress and the President both declared it to be a crisis and for nearly a decade there has been a flood of government-generated programs which were supposed to improve things. Some of these programs were quite massive and had effects upon health care which were certainly not anticipated. In their totality they have proven to be enormously expensive and appear not to have improved the nation's health or health care system commensurately. Much of what was started cannot be reversed. Health care planners, politicians, and of necessity doctors find themselves trying to work within a system which is developing serious internal frictions, lessened efficiency and higher costs. These problems seem to be compounded every time the planners and politicians try to tamper with the structure. There is a growing restiveness on the part of the health care professions and the health care industry.

Everyone is becoming frustrated. The government planners' plans are not working as expected. The government politicians find themselves getting deeper and deeper into something neither they nor their advisors seem to fully understand. Doctors find themselves trying to care for their patients amid a growing morass of often unnecessary and usually unworkable government regulations and constraints laid down by bureaucrats who have the authority, but unfortunately neither the knowledge nor the wisdom, to deal with the problems. To the frustrated planners and politicians, the entire health care system, and particularly the frustrated physicians who are its energizing force, must seem balky if not indeed stubborn and intransigent. This appears to be the case if one judges by the government's decision to use the carrot-and-stick approach, as though the health care system and the people who must try to make it work are some kind of dumb brutes. They are not, of course, and for this reason this approach will not work, but the attempt will surely be costly.

It is not certain whether the carrot-and-stick strategem ever really worked very well, even with donkeys. However this may be, this dumb-brute approach ignores the intelligence of a sophisticated, compassionate and generally dedicated health care profession. In fact, it is little short of insulting. Neither doctors, nor their patients, nor the health care system are likely to respond as might a donkey to the driver's whim expressed through the dangling of a never quite attainable carrot or to the prodding of a stick, no matter how vigorously applied. As intelligent human beings, they will always distrust incentives designed to fulfill someone else's purpose, and they will instinctively resist, resent and evade efforts to coerce and compel them to do another's bidding. The inevitable result will be a further increase of the friction within the health care system, a further loss in its efficiency, and yet higher costs. That this is true will eventually be discovered by the planners and politicians, but it now looks as though the cost of this discovery will be millions and perhaps billions of dollars to the taxpayer.

If the carrot-and-stick approach will not work, what will? It is suggested that what will work will have to be something which takes full advantage of the intelligence, knowledge, training and human compassion of the practicing doctor, and his very fundamental dedication to the betterment of

health and health care; and this includes a genuine concern with the fiscal aspects, if these can be shown to affect patient care adversely. This means that doctors and their professional organizations should be an integral part of the process of defining the problem and deciding what to do about it, and then be a part of the solution. The record clearly shows that when physicians and other health professionals become convinced (1) that a health problem exists, and (2) that the knowledge to do something about it is available, they soon become strong advocates of whatever must be done to solve the problem. But conversely, when they are not sure either of the diagnosis or of the treatment, they temporize, the cardinal rule then being to do no harm. There is room for this attitude and this approach in the government's effort to deal with the present health care crisis.

The medical profession has long since passed the horse-and-buggy stage. Carrots and sticks are for donkeys, not for doctors. If the problems of the health care system are to be solved, the friction within the system should be reduced, not increased; and the efficiency of the system should be improved, not reduced. There is much to be learned about how to do this better.

—MSMW

Death from Ischemia

DEATH HAS NOT BEEN a popular subject for research—perhaps, in part, for psychological reasons. There may be a feeling that the step from life to death cannot be measured in the laboratory, or assessed in terms of standard deviations and p values. And perhaps there is a sense of inevitability about death that seems to preclude intervention and therefore discourages investigation. Certainly it is too complex a subject to be approached, at present, with the techniques of the molecular biologist. Yet there is reason to believe that this is an area in which further knowledge will provide a direct feedback for improved clinical care.

In the progression of changes involved in dying, the most interesting is the event that determines the "point of no return," for it is this that defines the instant of death and constitutes the prime target for therapeutic intervention. This first, irreversible step will be quite different depending upon whether one is considering the whole organism or a single cell, the organism being much more vulnerable because of the functional interdependence of its parts. Consider, for example, circulatory arrest. Without intervention, death becomes inevitable after about 30 seconds due to loss of function of the respiratory center. After another 2 minutes or so, a second, normally irreversible, event occurs—loss of myocardial function. If these first two functional failures are circumvented by therapeutic intervention, a third can be revealed—impaired perfusion of peripheral organs, probably appearing first in the brain. This is due in part to loss of normal neurogenic maintenance of arterial pressure,[1] but also to stasis-induced changes in the vasculature and its contents. This latter phenomenon is the subject of a review by Dr. Rex Jamison which appears elsewhere in this issue of THE WESTERN JOURNAL OF MEDICINE. A fourth change which may limit the reversibility of circulatory arrest, *in vivo,* is the alteration in the composition of the blood as a result of its exchange with ischemic cells.

It seems clear that all four of the above changes must be controlled before one can well examine the tolerance to ischemia of the cells themselves. One approach is to study the cellular response to ischemia *in vitro* (a study of the effect on the mammalian retina[2] is an example) but as yet virtually nothing is known about the nature of the first irreversible change at the cellular level. The overall problem appears to be layered, like an onion, with the successive critical events revealed only by demonstrating that their prevention will extend survival. Such studies seem eminently worth while. Jamison's review indicates their potential importance at the organ level, and there is already one example of a therapeutic resurrection at the cellular level.[3] Thus the study of death may have considerable significance for the maintenance of life.

ADELBERT AMES III, MD
Massachusetts General Hospital
Boston

REFERENCES

1. Kowada M, Ames A III, Majno G, et al: Cerebral ischemia. An improved experimental method for study; cardiovascular effects and demonstration of an early vascular lesion in the rabbit. J Neurosurg 28:150-157, 1968

2. Ames A III, Gurian BS: Effects of glucose and oxygen deprivation on function of isolated mammalian retina. J Neurophysiol 26:617-634, 1963

3. Harris JW, Kellermeyer RW: The Red Cell. Cambridge; Harvard University Press, 1970, pp 481-486

Venous Thrombosis—Newer Diagnostic and Therapeutic Approaches

A CLINICAL CONFERENCE on venous thromboembolism is published elsewhere in this issue of THE WESTERN JOURNAL OF MEDICINE. Dr. Arthur J. Silvergleid of Stanford University School of Medicine describes newer techniques for the diagnosis of venous thrombosis, considers the problem of prophylactic therapy and discusses methods for using heparin in the treatment of established thrombosis. Since venous thrombosis occurs as a complication of a wide variety of medical and surgical illnesses, physicians in many branches of medicine should find the transcript of this conference worth their review.

Dr. Silvergleid summarizes the advantages and limitations of five diagnostic procedures for venous thrombosis: venography, the Doppler ultrasound flow study, impedance phlebography, radionuclide venography with technetium-sulfur labeled macroaggregates of albumin and external scanning of the legs after administration of ^{125}I-fibrinogen. The newer techniques are still under investigation and not generally available. The oldest procedure, venography, is widely available but probably under-utilized because of some degree of patient discomfort. In experienced hands[1] venography provides a reliable evaluation of the deep venous system, and it serves as the standard for comparing the accuracy of the newer methods. Venography has proven particularly valuable in patients with superficial thrombophlebitis in whom physical findings suggest associated deep venous involvement. It may also provide very useful information in a patient with minor leg signs suggestive of deep venous thrombosis who has a relative contraindication to the use of anticoagulants. In addition, Dr. Silvergleid advocates venography for patients with proven pulmonary embolism in order to define risk potential for future emboli. I suspect, however, that most physicians will settle for the pragmatic approach of administering anticoagulant therapy for from three to six months to such patients without delineating the extent of underlying venous disease.

The Doppler procedure should become increasingly available as diagnostic methods using ultrasound spread throughout the practicing community. As Dr. Silvergleid points out, this simple, rapid, non-invasive test helps particularly in the evaluation of a patient with an acutely swollen lower leg. Further data are needed to compare the findings obtained by the Doppler technique with the results of venography in patients who have minor leg signs suggestive of posterior tibial or superficial femoral vein thrombosis.

Studies with ^{125}I-fibrinogen scans, primarily in Britain, have added remarkably to our understanding of the incidence, pathogenesis, and therapy of venous thrombosis. Because of the risk of transmitting hepatitis with fibrinogen, use of this technique has been limited in the United States to a few clinical studies such as those currently in progress at Stanford. Although obviously destined for an expanded role in the clinical investigation of venous thrombosis, the place of ^{125}I-fibrinogen scans as a diagnostic method for general use in patient care has not yet been defined.

The ^{125}I-fibrinogen technique has revealed a startlingly high incidence of thrombi in small calf veins in surgical patients, orthopedic patients and patients with myocardial infarction. Such thrombi will develop in about 30 percent of patients over 40 years of age after major operations, and in a small but significant number of patients these small thrombi will extend cephalad to give rise to clinically significant thrombosis in the posterior tibial and superficial femoral veins. Understandably, attention has turned to an evaluation of prophylactic therapies capable of reducing the incidence of positive postoperative scans. Drugs impairing platelet function have been without such prophylactic effect to date, whereas small doses of heparin have been strikingly effective. These results support the pathologic studies of Sevitt,[2] which strongly suggest that accumulation of activated clotting factors in areas of stasis, rather than accumulation of platelets upon areas of injured endothelium, represents the key pathogenetic event triggering the formation of venous thrombi.

A low dose heparin schedule which has proven prophylactically effective in the general surgical patient—5,000 international units given subcutan-

eously two hours before operation and every 12 hours for the next five to seven days—does not increase clinical bleeding and does not prolong the activated partial thromboplastin time test beyond the normal range. Thus, the obvious question arises: Should surgical patients routinely receive prophylactic heparin? Although this question is discussed in the Stanford clinical conference, a conclusion is not reached. An editorial by Wessler and Yin[3] is quoted; the physician attempting to answer this question for his own patients should read that excellent editorial carefully. A very recent report by Gallus, Hirsh and Gent[4] raises the possibility that a short preoperative activated partial thromboplastin time test will help to identify which surgical patients should receive prophylactic heparin. I believe that prophylactic low dose heparin should be given to a patient over 40 years of age undergoing thoracic, abdominal or pelvic surgery if (1) the patient has a history or physical findings suspicious in any way of venous disease of the legs, or (2) the patient is grossly overweight, or (3) the patient has a short preoperative partial thromboplastin time, for example, a time of less than 36 seconds by the kaolin-activated technique. Unfortunately, small doses of prophylactic heparin will not prevent venous thrombosis in some groups of high-risk patients—namely, patients undergoing open prostatectomy or reconstructive hip procedures and patients with fractured hips. Full anticoagulation with warfarin has been recommended as the best method of providing effective prophylaxis against thromboembolism for these groups of patients.[5]

One must never confuse prophylactic and therapeutic heparin dosage schedules. When a thrombosis has already formed, much more heparin must be given, and it should be given intravenously, not subcutaneously. Either an intermittent or a continuous intravenous technique may be used. Basu and coworkers[6] have clearly shown that a continuous intravenous method provides effective therapy for venous thrombosis with minimal risk of bleeding. Jick and associates[7] in an earlier paper, which summarizes experience in three hospitals with an intermittent technique, reported a higher incidence of bleeding. Whatever method is used, two taboos must not be broken if bleeding is to be kept at a minimum. First, the heparinized patient must not receive intramuscular injections. Second, the heparinized patient must not be given drugs containing aspirin because such drugs impair platelet function. No data have yet appeared in which the same investigators, keeping all other factors constant, have compared intermittent and continuous intravenous heparin administration for therapeutic effectiveness and incidence of bleeding. Hence the results of the study described by Dr. Silvergleid which is currently in progress at Stanford are awaited with much interest.

SAMUEL I. RAPAPORT, MD
Professor of Medicine
Head, Hematology Division
University of Southern California
School of Medicine, Los Angeles

REFERENCES

1. Almen T, Nylander G: False signs of thrombosis in lower leg phlebography. Acta Radiol (Diagn) (Stock) 2:345-352, 1964
2. Sevitt S: Pathology and pathogenesis of deep vein thrombosis, chap 2, *In* Poller L (Ed): Recent Advances in Thrombosis. Edinburgh and London, Churchill Livingstone, 1973, pp 17-38
3. Wessler S, Yin ET: Theory and practice of minidose heparin in surgical patients—A status report (Editorial). Circulation 47: 671-676, 1973
4. Gallus AS, Hirsh J, Gent M: Relevance of preoperative and postoperative blood tests to postoperative leg-vein thrombosis. Lancet 2:805-809, Oct 13, 1973
5. Clagett GP, Salzman EW: Current concepts: prevention of venous thromboembolism in surgical patients. N Engl J Med 290: 93-96, Jan 10, 1974
6. Basu D, Gallus A, Hirsh J, et al: A prospective study of the value of monitoring heparin treatment with the activated partial thromboplastin time. N Engl J Med 287:324-427, Aug 17, 1972
7. Jick H, Slone D, Borda IT, et al: Efficacy and toxicity of heparin in relation to age and sex. N Engl J Med 279:284-286, Aug 8, 1968

"Trauma Rounds"

WITH THIS ISSUE a new feature appears in THE WESTERN JOURNAL OF MEDICINE. "Trauma Rounds," to be found elsewhere in these pages, reflects a long overdue need to give a truly epidemic health care problem the recognition it deserves in a journal of general medical interest. Trauma is a most important cause of disability and even death for those who are its victims. Trauma is also a most important factor in the ever rising health care costs as the science and technology of dealing with trauma improve. It is worthy of the close attention of all physicians if for no other reason than that they or their loved ones may be its victims with no advance notice at all.

We present "Trauma Rounds" in the confident expectation that they will make an important contribution to the medical literature in this field.

CASE REPORTS

Refer to: Gitnick GL, Hantman DI, Madden SC: Eradication of hepatitis B antigen in fulminant hepatitis. West J Med 120:241-244, Mar 1974

Eradication of Hepatitis B Antigen in Fulminant Hepatitis

GARY L. GITNICK, MD
DAVID I. HANTMAN, MD
SIDNEY C. MADDEN, MD
Los Angeles

A NEED FOR effective treatment of fulminant fatal hepatitis is clear. Occasional effectiveness or transient responses have been attributed to the use of exchange transfusion,[1,2] steroids,[3] heterologous liver perfusion[4-6] or cross circulation.[7] The transfusion of plasma or gamma globulin containing antibody to Hepatitis B Antigen (HBAg) has recently been advocated.[8] In theory the passive administration of antibody to HBAg, if given in sufficient quantity, should neutralize circulating virus, inhibit active tissue destruction, restrain continuing activity of virus-induced hepatic disease and allow hepatic regeneration to proceed. Among the dangers in this approach is the possibility of the formation of cytotoxic antigen-antibody complexes which might produce further acute or chronic liver damage, or might damage other organs such as the kidneys,[9] or joints.[10] This report describes the results of passive transfusion of HBAg *antibody* (HBAb) to a patient with fulminant hepatitis.

From the Division of Gastroenterology, Department of Medicine, and the Department of Pathology, University of California, Los Angeles, Center for the Health Sciences.

This study was supported in part by USPHS Research Grants 1-SOL-FR-05354 and 1-T1-A1-309, and General Research Support Grant RR-05354.

Submitted, revised, September 18, 1973.

Reprint requests to: G. L. Gitnick, MD, Department of Medicine, UCLA Center for the Health Sciences, Los Angeles, CA 90024.

Methods

Patients with hemophilia were tested for HBAb by complement fixation[11,12] and counterelectrophoresis.[13,14] The presence of HBAb was later confirmed by hemagglutination.[15] Plasmaphoresis was performed on donors with HBAb titers over 1:8 by counterelectrophoresis and over 1:16 by complement fixation and the plasma was stored at -20°C. Shortly before transfusion, plasma was thawed and crossmatching was performed. Because of subtype incompatibilities it was necessary to test plasma from several donors before compatible plasma was found. The complement fixation titer of antibody in each of the plasma units eventually used was 1:32.

HBAg tests were performed on each of the serial sera obtained from the patient. The patient was tested for HBAg and for HBAb, using immunodiffusion,[16,17] complement fixation,[11,12] counterelectrophoresis,[13] hemagglutination inhibition and hemagglutination.[15] End points were determined by testing serial two-fold dilutions of the test sera.

Standard procedures were used for the determinations of bilirubin,[18] glutamic oxaloacetic transaminase and glutamic pyruvic transminase,[19] alkaline phosphatase and prothrombin.

Patient Summary

A 33-year-old Caucasian woman was transferred to this hospital in stage IV[1] coma. She had been in good health until, five months before admission, a Papanicolaou smear showed grade III cells. Her physician advised hysterectomy and the operation was done at another hospital. Postoperatively, vaginal bleeding developed and she was given nine units of blood. She had no complaints in the subsequent weeks until one month before the present admission, when easy fatiga-

bility and malaise developed. Four days before this admission sore throat developed and the temperature rose to 38°C (100.4°F). The patient was admitted to another hospital and was noted to be icteric. Jaundice deepened and she became restless, hostile and uncooperative. She was given prochlorperazine (Compazine®), chlordiazepoxide hydrochloride (Librium®) and one intramuscular injection of 50 mg of meperidine (Demerol®). Because of recurrent vomiting and nausea, she was given trimethobenzamide hydrochloride (Tygan®). She gradually became somnolent and unresponsive on the evening before transfer to this hospital. The following morning she was not responsive to painful stimuli and was deeply jaundiced. She then was transferred to this institution.

On admission, the temperature was 37°C, the pulse regular at 128 per minute, respirations 16 per minute, and blood pressure 130/80 mm of mercury. The patient was comatose, jaundiced, and unresponsive to deep pain. Fetor hepaticus was present. The skin was yellow but spider nevi or other stigmata of chronic liver disease were absent. The conjunctivi were icteric and the pupils were dilated but reacted to light. On funduscopic examination the discs were flat and there were no retinopathic changes. No abnormalities of the ears, nose, mouth, throat or neck were noted. Lymph nodes, breasts, chest and heart were within normal limits. The abdomen was soft and not distended. Bowel sounds were present; no bruits were heard. The liver was palpated 2 cm below the right costal margin and percussion revealed its span to be 11 cm in the midclavicular line. The spleen was not palpated. No other masses were felt. On rectal examination brown stool was noted in the rectum. Extremities were free of peripheral edema or acute or chronic joint changes.

Results of laboratory studies on admission were: alkaline phosphatase, 18 King-Armstrong units (normal 4 to 7); SGOT, 610 international units per ml (normal 10 to 40); SGPT, 440 international units per ml (normal 5 to 35); bilirubin: total 33 grams, direct 25 grams; prothrombin, 13.5 percent; amylase, 94 mg per 100 ml (normal 60 to 180); sodium, 136 mg per ml; potassium, 3.6 mEq, chloride, 102 mEq and CO_2, 23.5 mEq per liter; creatinine, 0.6 mg and glucose, 102 mg per 100 ml; calcium, 4.4 mEq and phosphorus, 0.7 mEq per liter; placidyl level, 0.4 mg per 100 ml (normal); and screen for hypnotic drugs negative. A nasogastric tube was passed and guaiac-negative clear gastric juice was aspirated. As the tube was passed, the patient transiently seemed responsive to vocal stimuli but rapidly became unresponsive to all stimuli, including pain. Magnesium sulphate was given through the tube, followed in two hours with 2 grams of neomycin and thereafter 1 gram of neomycin every six hours. Aquamephyton®, 20 mg subcutaneously, was given every 24 hours.

Six hours after admission the hematocrit had fallen from 35 percent to 23 percent and prothrombin concentration had fallen to 10 percent. Partial thromboplastin time was 92.5 seconds (control 37.8 seconds). Coffee-ground material was continuously aspirated from the stomach. Two units of fresh frozen plasma and 3 units of factor IX (Konyne®) were administered. Six hours later the prothrombin concentration had risen to 30 percent but platelets numbered 58,000 per ml. Again 24 hours after admission, prothrombin concentration was 10 percent. Partial thromboplastin time was 133 seconds and the platelet count had fallen to 18,000 per ml. The patient then received six units of Konyne®, three units of fresh blood and six platelet packs. Coffee-ground guaiac-positive material was still present in the nasogastric aspirate. The liver span as determined by percussion had now decreased to no more than 4 cm in the midclavicular line.

Two units of plasma, each containing HBAb were administered separately over a three-hour period after the patient had been in stage IV coma for 41 hours. Twelve hours later she made spontaneous movements and responded to pain but not to oral commands. This minor change in the level of consciousness was uninterpretable. The nasogastric aspirate became clear and guaiac-negative, but the urine output slowed to 20 to 30 ml per hour and the creatinine rose to 2.9 mg per 100 ml. Furosemide was given intravenously and the urine output rose to 60 ml per hour. The central venous pressure varied between 12 and 18 mm of water. The patient began having difficulty in clearing oral and tracheal secretions, and Kussmaul breathing was noted concomitant with the detection of metabolic alkalosis. She was also found to have a massive hematoma under the tongue. Tracheostomy was performed and intermittent positive pressure breathing was administered. Sixty hours after admission, acute respiratory distress developed. Moist rales were present in all lung fields. Neck veins were distended. Digoxin

(0.25 mg) was given slowly intravenously. Sixty minutes later cardiac arrest occurred and did not respond to resuscitative efforts.

Pathologic Studies

Autopsy was delayed and then was performed by the coroner's office. Jaundice and edema were severe. Bilateral hydrothorax and pronounced pulmonary congestion and edema were noted. The lungs combined weighed 1,450 grams. The liver was shrunken to half normal size, weighing 680 grams. It was yellow-brown with focal deep red areas. Microscopically it showed massive almost total destruction of hepatocytes, very few persisting as fragmented cords. Bile ductules, somewhat increased in number, helped identify the portal tracts in a generally edematous matrix of cell debris and fibrils. The spleen was soft and weighed 300 grams. No sections were available. The uterus was surgically absent. The kidneys appeared normal grossly and on microscopic examination.

Serologic Studies

Circulating HBAg was detected in the serum on admission, with a complement fixation titer of 1:256. Anticomplementary activity was absent before and after antibody infusion. Antigen was also detected by hemagglutination inhibition, and by counterelectrophoresis. Antibody was not detected by any of these methods. Forty-one hours after admission, and immediately before the administration of the antibody to HBAg, the serologic findings were unchanged. Seventy minutes after infusion of the first unit of hyper-immune plasma had been started (125 ml of it having been infused by that time) a serum specimen was free of HBAg as determined by complement fixation, counterelectrophoresis, hemagglutination inhibition and radioimmunoassay. Specimens of serum taken one, two and three hours later, and post mortem, remained free of HBAg.

Antibody to HBAg was first detected 120 minutes after the first plasma infusion was started, and it was present in each of the subsequent specimens. Circulating anticomplementary activity was not detected. The infused HBAb was capable of producing a precipitate when added to the patient's serum in agarose immunodiffusion plates.

Twenty-four hours after the administration of antibody, the patient's serum creatinine rose and the urine output fell. Red blood cell casts were not present in serial urine specimens. At that time circulating antibody levels could be detected by the hemagglutination test, but antigen was not detectable by any of the assay systems. Anticomplementary activity was absent, and there was no evidence of circulating immune complexes. Serum complement levels were not determined.

Comment

The administration of antibody to Australia antigen resulted in the rapid clearance of all circulating antigen within 60 minutes after the beginning of antibody infusion. This clearly points to the ability of small quantities of antibody either to alter or to complex with circulating antigen. Current data do not provide information as to the effect of antibody on antigen within liver cells. Although available data suggest the clearing of all antigen from the peripheral circulation, the possibility exists that in this patient the administration of antibody resulted in the development of circulating immune complexes which, in turn, may have led to the progression rather than the amelioration of the illness. The postulate that immune complexes may have been induced is hypothetical. Our studies indicate the absence of antigen in association with antibody and the absence of anti-complementary activity. These findings would weigh against the likelihood of circulating immune complexes.

The neutralization of circulating antigen may provide some hope for future approaches to the treatment of fulminant hepatitis. In the case here reported, it is conceivable that the patient would not have died if antibody had been administered earlier in the course of illness. In theory, infusion of HBAb early in the course of viremia would give the greatest chance of success. Though the administration of antibody does not provide support for a failing liver nor replace destroyed liver cells, HBAb may help remove sources of continuing activity and hence lessen the destruction of liver cells. This could give the liver a chance to regenerate if it still has capacity to do so. The current data support the concept that the administration of HBAb may remove HBAg from the circulation. A controlled prospective double-blind trial of HBAb in fulminant hepatitis has been undertaken.

Summary

Plasma containing hyper-immune human antibody to Hepatitis B Antigen (HBAg) was adminis-

tered to a 32-year-old woman with HBAg-positive fulminant hepatic failure. It was given after she had been in stage IV coma for 41 hours, and although all circulating HBAg then rapidly cleared from the peripheral circulation, she died in hepatic coma two and a half days later with signs of congestive heart failure. Massive hepatic necrosis was found at autopsy.

The administration of plasma containing hyperimmune antibody to HBAg may be helpful in clearing circulating antigen from the blood and may be a useful approach to be investigated further in the management of fulminant hepatitis.

REFERENCES

1. Trey C, Burns DG, Saunders SJ: Treatment of hepatic coma by exchange blood transfusions. N Engl J Med 274:473-481, 1966

2. Graham JH, McGoldrick DM, Stohlman F Jr: Exchange transfusion in the treatment of fulminating hepatitis. N Engl J Med 274:497-499, 1966

3. Katz R, Velasco M, Klinver J, et al: Corticosteroids in the treatment of acute hepatitis in coma. Gastroenterology 42:258-265, 1962

4. Eiseman B: Treatment of hepatic coma by extracorporeal liver perfusion. Ann Roy Coll Surg Eng 38:329-348, 1966

5. Bosman SC, Terblanche J, Saunders SJ, et al: Cross-circulation between man and baboon. Lancet 2:583-588, 1968

6. Hume DM, Gayle WE Jr, Williams GM: Cross-circulation of patients in hepatic coma with baboon partners having human blood. Surg Gyn Obstet 128:495-517, 1969

7. Gutman RA, Leinbach GE, Thomas ED, et al: Acute hepatic coma treated by cross-circulation or exchange transfusion. N Engl J Med 276:933-935, 1967

8. Eigenbrodt EH, Barrera A, Hull AR, et al: Glomerulonephritis with deposition of Australia antigen-antibody complexes in glomerular basement membrane. Lancet 2:234-237, 1971

9. Combes B, Stastny P, Shorey J: Fulminant hepatitis treated with serum containing antibody to Australia antigen. N Engl J Med 284:919, 1971

10. Alpert E, Isselbacher KJ, Schur PH: The pathogenesis of arthritis associated with viral hepatitis. N Engl J Med 285:185-189, 1971

11. Shulman NR, Barker LF: Virus-like antigen, antibody, and antigen-antibody complexes in hepatitis measured by complement fixation. Science 165:304-306, 1969

12. Wong DC, Morrow AG, Chanock RM: A complement fixation test for measuring Australia antigen and antibody. J Infec Dis 120:383-386, 1969

13. Gocke DJ, Howe C: Rapid detection of Australia antigen by counter-immunoelectrophoresis. J Immun 104:1031-1034, 1970

14. Prince AM, Burke K: Serum hepatitis antigen (SH): Rapid detection by high voltage immunoelectroosmophoresis. Science 169:593-595, 1970

15. Vyas GN, Shulman NR: Hamagglutination assay for antigen and antibody associated with viral hepatitis. Science 170: 332-333, 1970

16. Allison AC, Blumberg BS: An isoprecipitation reaction distinguishing human serum-protein types. Lancet 1:634-637, 1961

17. Blumberg BS, Alter HJ, Visnich S: A "new" antigen in leukemia sera. JAMA 191:541-546, 1965

18. Simmons NA: An automated method for serum bilirubin determination. J Clin Path 21:196-201, 1968

19. Rutman S, Frankel S: A colorimetric method for the determination of serum glutamic oxaloacetic and glutamic pyruvic transaminase. Am J Clin Path 28:56-63, 1957

Refer to: Pasternak DP: Hemochromatosis presenting as diabetic ketoacidosis with extreme hyperglycemia. West J Med 120:244-246, Mar 1974

Hemochromatosis Presenting as Diabetic Ketoacidosis with Extreme Hyperglycemia

DERICK P. PASTERNAK, MD
Burlingame, California

DIAGNOSING HEMOCHROMATOSIS is frequently difficult because of its features mimicking other more common diseases, such as hepatic cirrhosis, diabetes mellitus or heart failure.[1] Even when these conditions coexist, and the index of suspicion should be high, there may be other features, such as chronic alcoholism, which may obscure the true cause of the patient's disease. As a consequence the diagnosis may not be established until the postmortem examination. This report describes a case illustrating these difficulties, and in which there was the further and unusual factor of diabetic ketoacidosis with extreme hyperglycemia to an extent hitherto unreported in this condition.

CASE: A 60-year-old man entered the hospital emergency room 27 November 1970 with complaint of vomiting and lethargy which had lasted for four days. During this time he had become progressively more lethargic, and had refused most nourishment prepared by his wife. No history of polyuria could be elicited, but he did consume large amounts of beer just before becoming ill. This was apparently not unusual for him. The past history included malaria contracted during World War II. The patient took no medications, had had no transfusions and drank no wine. Family history was unobtainable.

On physical examination the patient was observed to be cachectic and drowsy, but arousable. His breath had a fruity odor. The pulse rate was 106 per minute, respirations 30 per minute, blood

From the Dunham Army Hospital, Carlisle Barracks, PA.
Submitted July 11, 1973.
Reprint requests to: D. P. Pasternak, MD, 741 Linden Avenue, Burlingame, CA 94010.

pressure 80/60 mm of mercury and body temperature 35.6°C (96°F). The skin was dry; there was one spider angioma in the sternal notch, but no icterus or other pigment abnormality. General physical examination was unremarkable, except for dry mucous membranes and a large, firm and nodular liver. On neurological examination, the patient was oriented as to name and place, but not as to date; reflexes were hypoactive; there were no localizing signs or asterixis.

Admission laboratory data showed a hematocrit of 45 percent and leukocyte count of 8,600 per cu mm with a normal differential. Blood glucose concentration was 2,700 mg per decileter (dl), serum sodium 154, potassium 5.0, chlorine 106, CO_2 combining power 11 mEq per liter. Serum acetone was 4+; no dilutions were done. Blood urea nitrogen was 35 mg per dl. The prothrombin time was 15 seconds (control 12 seconds). The urine was straw colored and clear with 4+ sugar and acetone, no protein, 2 to 3 red blood cells and 5 to 8 white blood cells per high power field; there were no casts or bacteria seen. An x-ray film of the chest showed hyperinflated lungs, normal sized heart and no pulmonary infiltrate. The electrocardiogram showed occasional atrial and ventricular premature beats, low voltage and nonspecific ST segment abnormalities. Guaiac tests of the stool were negative.

Bed rest was prescribed and hypotonic saline solution was given intravenously at the rate of 1,000 ml per hour. Insulin was also administered intravenously and after two hours potassium chloride was added to the intravenous fluids. After 4 liters of fluid and 200 units of crystalline insulin the blood glucose was 1,260 mg per dl, CO_2 combining power 18 mEq per liter, serum acetone 4+, urine sugar 4+, urine acetone 2+. During the first seven hours of therapy, the patient received a total of 7,000 ml of fluids, 310 units of crystalline insulin, 200 mEq of potassium, and 540 mEq of sodium. The blood pressure then was 125/65 mm of mercury, pulse rate 100 per minute, the hematocrit 34 per cent, blood glucose 720 mg per dl, potassium 5.2 mEq per liter, CO_2 combining power 19 mEq per liter, serum acetone trace, urine sugar 4+, urine acetone 1+. The urine output was 3,200 ml in the first seven hours.

On the following morning the patient became gradually more disoriented and had hallucinations. Chlordiazepoxide was given for presumed delirium tremens. During the ensuing 24 hours under continuing insulin and fluid therapy the blood glucose gradually fell to 220 mg per dl. He coughed up greenish purulent sputum. On the third hospital day disorientation and coughs producing sputum persisted and the patient's temperature rose to 38.8°C (101.84°F). Blood, sputum and urine cultures were taken. A lumbar puncture yielded clear and colorless fluid under an opening pressure of 110 mm of water; there were no cells, sugar content was 157 mg per dl (simultaneous blood sugar 220 mg per dl) and protein 44 mg per dl; the fluid was cultured. An analysis of the urine showed a trace of protein, 2+ sugar, no acetone and 15 to 20 white blood cells. The patient was given cephaloridine, 1 gram administered intramuscularly every six hours. Despite this his condition continued to deteriorate. Cheyne-Stokes respirations and pulmonary edema developed and he died on the fourth day following admission to hospital. An x-ray film of the chest on the last day of life showed no infiltrate. All cultures were sterile.

Autopsy 12 hours after death showed no gross abnormalities of the heart; the lungs were edematous; the gastrointestinal tract was normal; the liver weighed 2,000 grams, was dark brown, finely nodular, and very firm; the spleen was minimally enlarged with pulp hyperplasia; there was an area of softening in the right kidney; the endocrine organs were grossly normal; in the brain, the tip of the left temporal lobe was absent. Microscopically examined, the liver showed cirrhosis with large amounts of brown pigment reacting with Prussian blue stain present in the portal triads, hepatic cells and sinusoids. There was no evidence of significant coronary atherosclerosis; iron was found in the myocardial fibers, as well as in the epicardial tissues and in the interventricular septum. The lungs had edema fluid in the alveoli and there was a neutrophilic exudate in the basal portion. The pancreas had large amounts of iron deposited both in the acinar tissues and in the islets of Langerhans. Iron deposits were also found in the stomach (epithelium), spleen, thyroid, adrenals (primarily the zona glomerulosa of the cortex) and kidneys (tubular epithelium). In addition, the right kidney had a focus of acute pyelonephritis and there were several areas containing sclerotic glomeruli and interstitium infiltrated with lymphocytes and plasma cells. In these areas the tubules were dilated and contained amorphous eosinophilic material. The pituitary gland had been submitted to the National Pituitary Bank and was not examined microscopically.

Comment

The post mortem examination clearly established that this patient had idiopathic hemochromatosis. The pattern of iron deposition is characteristic, and there was no history of multiple transfusions or excessive iron ingestion.[1-3] The disease usually presents as cirrhosis, or diabetes, or both[1,4] as in this patient; the appearance of diabetes of this severity is distinctly unusual, however. In a recent review of diabetes in 115 patients with hemochromatosis, Dymock et al[5] quoted no cases of ketoacidosis. Although the older literature is replete with cases of diabetic ketoacidosis in hemochromatosis, many of these reports originated in the pre-insulin era.[6,7]

The relative ease with which this patient's diabetic ketoacidosis was brought under control despite the extreme hyperglycemia is interesting in view of the intermittent reports in the literature of insulin resistance in patients with hemochromatosis.[7-9] It is by no means a constant finding, however.[5,10] Similarly, in view of the current controversy as to whether hemochromatosis "protects" against the atherosclerotic complications of diabetes[11,12] or does not,[5,13,14] it is relevant to point out that the patient under discussion had no retinopathic changes, only minimal coronary atherosclerosis, and the glomerular sclerosis noted in the kidneys was more compatible with chronic interstitial nephritis or chronic pyelonephritis than with the glomerulosclerosis associated with diabetes.[15]

The question of how this extreme of hyperglycemia was reached in the present case cannot be answered with any degree of certainty. Blood sugar in the range of 2,000 mg per dl and above has been described primarily in association with hyperosmolar nonketotic coma[16] but there have been occasional cases of ketoacidosis with extremely high blood sugar.[17-20] Most of these patients had received large amounts of glucose by vein,[18,19] or by mouth in the form of Coca-Cola syrup,[20] after what in retrospect had clearly been the onset of their diabetic ketoacidosis.

No such history could be elicited from this patient or his wife, but neither of them was a reliable enough historian under the circumstances. It seems reasonable to postulate that shortly before admission the patient did in fact ingest large amounts of carbohydrate, thereby acutely elevating his blood sugar to extreme levels because of the lack of circulating insulin in his state of already existing moderate diabetic ketoacidosis.

Summary

A 60-year-old alcoholic male patient presented in diabetic ketoacidosis with extreme hyperglycemia—2,700 mg per dl, a level previously unreported in this setting. After ketoacidosis had been adequately controlled delirium tremens and heart failure developed and the patient died. At post mortem examination, hemochromatosis was found.

REFERENCES

1. Finch SC, Finch CA: Idiopathic hemochromatosis—An iron storage disease. Medicine 34:381-430, Dec 1955

2. Wyatt JP: Patterns of pathological iron storage—I. The nature and significance of transfusional siderosis and its relationship to idiopathic hemochromatosis and allied conditions. AMA Arch Path 61:42-55, Jan 1956

3. Wyatt JP: Patterns of pathological iron storage—II. Exogenous siderosis in chronic anemia due to prolonged oral iron medication. AMA Arch Path 61:56-61, Jan 1956

4. Pollycove M: Hemochromatosis, *In* Stanbury JB, Wyngaarden JB, Frederickson DS: The Metabolic Basis of Inherited Disease, 3rd Ed. New York, McGraw-Hill, 1971, pp 1051-1086

5. Dymock IW, Cassar J, Pyke DA, et al: Observations on the pathogenesis, complications, and treatment of diabetes in 115 cases of hemochromatosis. Am J Med 52:203-209, Feb 1972

6. Sheldon JH: Haemochromatosis. London, Oxford University Press, 1935

7. Althausen TL, Kerr WJ: Hemochromatosis—A report of three cases with results of insulin therapy in one case. Endocrinology 11:377-412, Sep-Oct 1927

8. Eskind IB, Franklin W, Cowell FC: Insulin-resistant diabetes mellitus associated with hemochromatosis. Ann Int Med 38: 1295-1305, June 1953

9. Buchanan J, Young ET: Insulin resistance in haemochromatosis. Postgrad Med J 42:551-554, Sep 1966

10. Althausen TL, Doig RK, Weiden S, et al: Hemochromatosis. AMA Arch Int Med 88:553-570, Nov 1951

11. Lonergan P, Robbins SL: Absence of intercapillary glomerulosclerosis in the diabetic patient with hemochromatosis. N Engl J Med 260:367-370, Feb 1959

12. Pirart J, Barbier P: Effect protecteur de l'hemochromatose vis-a-vis des lesions vasculaires seniles ou diabetiques. Diabetologia 7:227-236, Aug 1971

13. Becker D, Miller M: Presence of diabetic glomerulosclerosis in patients with hemochromatosis. N Engl J Med 263:367-373, Aug 1960

14. Griffiths JD, Dymock IW, Davies EWG, et al: Occurrence and prevalence of diabetic retinopathy in hemochromatosis. Diabetes 20:766-770, Nov 1971

15. Freedman LR: Urinary tract infection, pyelonephritis, and other forms of chronic interstitial nephritis, *In* Strauss MB, Welt LG (Eds): Diseases of the Kidney, 2nd Ed. Boston, Little, Brown, & Co., 1971, pp 667ff

16. Knowles HC: Syrupy blood. Diabetes 15:760-761, Oct 1966

17. Lawrence RD: Extreme hyperglycemia in diabetic coma. Br Med J i:377, Mar 1934

18. Meyer PC, Salt HB: Unusually high blood sugar in a boy. Br Med J i:171-172, Jan 1951

19. Fromantin M, Gauthier M, Boisselier P, et al: Coma inaugural d'une diabete juvenile aigu avec glycemie a 23 grammes. Diabete 17:91-94 Apr-Jun 1969

20. Bernet FW, Siegal A, Pasternak DP: Unpublished observations

Refer to: Bernard JD, Shearn MA: Psychogenic pseudo-Sjögren's syndrome. West J Med 120:247-248, Mar 1974

Psychogenic Pseudo-Sjögren's Syndrome

J. DAVID BERNARD, MD, *Stockton*
MARTIN A. SHEARN, MD, *San Francisco*

PATIENTS SOMETIMES simulate symptoms of disease states, apparently believing they will benefit somehow. The medical literature is replete with instances of factitious disease such as self-induced dermatitis, feigned chest pain in drug addicts, and extraordinary examples of Munchausen's syndrome.[1] Now that symptoms of relatively rare diseases, once known only to physicians, become familiar to laymen through the media, it is probable that we will encounter a wider variety of spurious disease.

The present report concerns a young woman with surreptitious self-induced vomiting, in whom parotid enlargement developed as a result of malnutrition. She feigned a perfect history for Sjögren's syndrome, thereby providing her physicians with an apparent explanation for the parotid enlargement. After the patient had confused a variety of medical specialists, a nurse happened to see her inducing vomiting. This observation finally permitted the proper diagnosis.

Report of a Case

A 19-year-old, white, single woman was admitted to the University of California Medical Center, San Francisco, with a history of parotid and submaxillary gland enlargement for two years. For one year she had had dryness of the mouth which necessitated constant sipping of fluids, especially during meals. She said that her eyes felt scratchy and dry, and although no abnormality had been found on ocular examination, an ophthalmologist had prescribed artificial tears. Eight weeks before admission, she reported that her fingers turned white on exposure to cold. She also complained of stiffness of the elbows, wrists and small joints of the hands, especially in the mornings. She specifically denied vomiting or any unusual attitude toward food. Although she lost 20 pounds in six months, she said that her appetite was good.

The patient had been seen by an intetrnist, two endocrinologists, a rheumatologist, and an ophthalmologist, and extensive laboratory studies had been made, some of them during a stay in hospital for that purpose, in efforts to explain the puzzling symptoms.

On physical examination the patient was observed to be thin; body weight was 37.2 kg (82 pounds). The only apparent abnormality was remarkable enlargement, without tenderness, of the parotid and submaxillary glands. Eyes, mucous membranes and joints appeared normal.

The first impression was that the patient had Sjögren's syndrome, manifested by arthralgia, Raynaud's phenomenon, dryness of eyes and mouth, and salivary gland enlargement. A complete workup, however, failed to show any abnormalities of the eyes or mouth; and responses to all immunological tests, so frequently positive in patients with Sjögren's syndrome,[2] were negative. A sequential salivary scintiscan with 99m-technetium pertechnetate showed no abnormality. Biopsy of the parotid gland and labial mucosa[3] failed to show any of the changes of Sjögren's syndrome, though it did show fatty infiltration. Another disturbing aspect of the case was persistent metabolic alkalosis; serum bicarbonate was as high as 41 mEq per liter and serum potassium was 2.5 mEq per liter, with the urine pH 7.0. Many other laboratory tests, evaluating all systems at least once and some systems several times, gave normal results.

After the patient had been in hospital two weeks, a nurse saw her inducing vomiting. The patient then admitted having done this at least three times daily for over two years. The alkalosis, which had been so puzzling, was explained by the persistent vomiting. The salivary gland enlargement was explained by fatty infiltration secondary to malnutrition. The complaints of dry mouth, dry eyes, joint symptoms, Raynaud's phenomenon, and arthralgia had been feigned. Having learned, at the time the parotid enlargement developed, that her physicians were considering the diagnosis of Sjögren's syndrome, the patient had learned all the symptoms of this disorder and had recited them at all subsequent examinations.

Psychiatric evaluation revealed a variety of

From San Joaquin General Hospital, Stockton, Kaiser-Permanente Medical Center, Oakland, and University of California, San Francisco.

Submitted July 16, 1973.

Reprint requests to: J. D. Bernard, MD, P.O. Box 1020, Stockton, CA 95201.

severe conflicts, many of which related to sexual identity. During a four-month period, the patient was seen in at least a dozen psychiatric interviews. The findings were typical of anorexia nervosa. She had fixed and compelling ideas about food and its ingestion, as well as a preoccupation with her body. Her character immaturity was likewise typical of the anorexia nervosa patient. Her family structure unwittingly tended to support her pathological emotional defenses. The patient intensely resented the unattractive parotid swelling and the facial edema, both of which fluctuated. She and her therapist were in complete agreement that the salivary gland enlargement was directly proportional to the amount of self-induced vomiting.

Discussion

Sjögren's syndrome is a chronic inflammatory disease characterized by dryness of the eyes and mouth and parotid enlargement, most often in association with a rheumatic disorder such as rheumatoid arthritis or systemic lupus erythematosus. A remarkable degree of immunological reactivity is frequently present. The salivary gland enlargement of Sjögren's syndrome is related to intensive lymphocytosis in the affected gland, and the diagnosis can be made with certainty by biopsy of that structure. The characteristic histologic features include massive lymphocytic infiltration, ductal alterations, and epimyoepithelial islands.

Other causes of parotid enlargement that must be distinguished from Sjögren's syndrome include cirrhosis of the liver, diabetes mellitus, malnutrition, and hyperlipoproteinemic states. The histologic feature common to these latter conditions, fatty infiltration, bears no resemblance to the findings in Sjögren's syndrome.[4] Examples of malnutrition states causing parotid enlargement include kwashiorkor, and deficiencies of vitamin A, vitamin C, or some of the B vitamins. Parotid enlargement has also been frequently observed in association with malnutrition in soldiers in prison camps, and was seen in some 3,000 malnourished people of Greece during the second World War.[5] The salivary gland enlargement in these malnutrition states usually differs in a number of ways from that seen in Sjögren's syndrome: the swelling tends to develop more slowly, and is usually asymptomatic; xerostomia tends to be minimal, with normal or only slightly diminished salivary flow. Ocular, rheumatic, and immunological features of Sjögren's syndrome are lacking. In cases of reasonable doubt, parotid biopsy readily distinguishes Sjögren's syndrome from these conditions. Other forms of bilateral salivary gland enlargement that may accompany some infectious diseases, Bocck's sarcoid and certain granulomatous disorders, can usually be excluded in view of the clinical setting in which they occur.

The patient discussed here presents an example of the confusion that may attend the differential diagnosis of salivary gland enlargement when essential ingredients of the history are lacking. Her ability to conceal her self-induced vomiting, coupled with her adoption of the symptoms of Sjögren's syndrome, misled her physicians and resulted in a remarkable array of laboratory tests, biopsies and therapeutic procedures before the correct diagnosis was finally made. There is a great tendency to underestimate the degree of unconscious compulsions and lack of ego control suffered by the patient with anorexia nervosa. It is most difficult to understand how an apparently non-psychotic, intelligent, attractive young woman would have virtually no "will power" in regard to her compelling food neurosis.

We are all aware of patients who feign the symptoms of coronary thrombosis, which are so well known by the laity. It seems that we may now begin to see spurious syndromes of a rarer sort presented by mentally unbalanced but medically sophisticated patients living in an era of medically oriented mass media. Psychogenic pseudo-Sjögren's syndrome appears to be an alliterative case in point.

Summary

A young woman afflicted with a compelling anorexia nervosa-like neurosis feigned the symptoms of Sjögren's syndrome. These included Raynaud's phenomenon, arthralgia, and dryness of the eyes and mouth and complemented her parotid enlargement, which had resulted from the malnutrition of self-induced vomiting. As knowledge of diseases is widely disseminated to the laity, physicians may well encounter more feigned examples of relatively uncommon disease states.

REFERENCES

1. Chapman JS: Peregrinating problem patients—Munchausen's syndrome. JAMA 165:927-933, 1957

2. Bloch KJ, Buchanan WW, Wohl MJ, et al: Sjögren's syndrome—A clinical, pathological, and serological study of sixty-two cases. Medicine 44:187-231, 1965

3. Talal N, Asofsky R, Lightbody P: Immunoglobulin synthesis by salivary gland lymphoid cells in Sjögren's syndrome. J Clin Invest 49:49-54, 1970

4. Shearn MA: Sjögren's Syndrome, Vol II in the series Major Problems in Internal Medicine, LH Smith Jr (Ed). Philadelphia, WB Saunders Company, 1971

5. Katsilambros L: Asymptomatic enlargement of the parotid glands. JAMA 178:513-514, 1961

LETTERS *to the Editor*

OMA's Continuing Education Program

To the Editor: "A Review of Mandatory Continuing Education in Oregon" in the first issue of The Western Journal of Medicine [Pennington M: West J Med 120:80-87, Jan 1974] has crystallized my thinking in regard to California's voluntary certification program. I would like to register a vote in favor of change. I strongly urge the California Medical Association to stop pussyfooting and with all due haste to institute a requirement of continuing education for active membership in the organization.

Frankly, I have not participated in the current voluntary system, reporting my continuing education and receiving a certificate, because the California program seems basically to be aimed at impressing the public and convincing government that any societal action to ensure quality medical care and upgrade physicians' postgraduate education is unnecessary. Further, it appears to be directed toward giving us the opportunity to pat ourselves on the back. In essence it seems to imply childish self-congratulation (see how many meetings I attended) or else to smack of grandstanding (look how qualified I am).

If continuing medical education is important —and I believe it is essential—then it is important enough to be required of all physicians who want to practice medicine, not just those who like to conform or who enjoy the recognition. Making it mandatory for continued membership in CMA is one route that would include most practicing physicians, but relicensure by the state at regular intervals would be even more inclusive. I believe we are only kidding ourselves if we think that a voluntary program is really going to improve the quality of care. Those who most need the impetus to continue their education are least likely to comply; a compulsory program would basically give continuing education the stature it merits.

Mary Riggs, MD
Los Altos, California

To the Editor: Someone sent me The Western Journal of Medicine article by Pennington on "Mandatory Continuing Education in Oregon" [Pennington M: A review of mandatory continuing medical education in Oregon. West J Med 120:80-87, Jan 1974]. It amuses me to think of someone saying "let's send this to Smith and see if it tugs on his chain." There are a few things more ridiculous than grown men indulging in kid's stuff and taking themselves seriously all the while. "Generating," as the author says, "masses of reports, studies, and surveys," the counsel on Medical Education in Oregon has succeeded in producing a gigantic fraud. The unknowing may think their doctors a better scholar for the program, but the opposite is more likely.

I was down in Ashland last summer during the Tomlinson Lectures in Medford, purely fortuitively with some non-medical friends to see the Shakespeare Festival plays, and I met a former Oregon Medical Association officer at the motel pool. He advised me to go over and "sign in anyway" for the lectures because even if I didn't want the points, I could then deduct the expenses from my income taxes. I wonder if he complains about President Nixon. The main thing that preserves excellence in physicians is pridè, and this is the sort of nonsense that saps this pride. What with the combination of foolishness and dishonesty in its leadership, one of the things I am proudest of is that I am not a member of the Oregon Medical Association.

Roger G. Smith, MD
Hillsboro, Oregon

Malpractice Awards

To the Editor: In a short article [Elmendorf T: From the past to the future. Calif Med 119:38-41, Dec 1973], Dr. T. Elmendorf, the president of the California Medical Association, referred to the public's "unreasonable expectations as to what medicine can do, and to the basic desire for

immortality" as important factors for the mushrooming number of malpractice suits.

In my opinion medical doctors and hospitals have been an object of discrimination of scandalous proportions.

The reasons are:

1. Availability of huge amounts of money from insurance carriers whose losses are covered by ever-increasing premiums.

2. The openhanded leniency of the courts to accept settlements for disproportionate and enormous amounts of money for claims against doctors and hospitals without consideration as to the impact of such settlements on society to a point where administration of justice is rapidly becoming a form of extortion.

3. The financial gains in store for successful trial lawyers—whose earnings from a single settlement have amounted up to 50 percent of sums awarded to the plaintiff.

What is a reasonable fee for a lawyer? Should the consumer have a say? Should there be upper limits for liabilities incurred during the delivery of medical care? Should spiraling insurance premiums go unchecked by the many who have to pay for the gains of the few? Why should doctors or anybody be subject to indignities while in court, and the most common principles of decency be ignored in order to impress the jury? Why should a medical doctor be discriminated against, be treated more harshly, and pay settlements, than those who commit premeditated capital crimes, political crimes, or those who are responsible for industrial or military negligence that has all too frequently cost millions of dollars and scores of lives?

If accountability is at stake, why should those courts who are responsible for the freedom of criminals known to be repeaters of serious crimes, or prison officials under whose management prisoners escape or suffer bodily harm by the hands of other jailmates, go unpunished?

Are the best interests of the public met by closing our eyes to these realities? I suggest:

1. A limitation by law on maximum allowance for settlements that does not discriminate against providers of medical care.

2. A professional conduct and peer review committee that includes consumer interests with enforcing power should be established for the lawyers, with power to establish equitable ranges of earnings.

OLGARD DABBERT, MD
San Diego

Traumatic Injury —A Health Care Crisis

TO THE EDITOR: I wish to compliment you for printing the article by Trunkey, Lim, and Blaisdell [Trunkey DD, Lim RC Jr, Blaisdell FW: Traumatic injury—A health care crisis. West J Med 120:92-94, Jan 1974] on the neglected health care crisis of trauma. Their delineation of the problem was dramatic, accurate, and timely. Inevitably, however, outlining the solution is far more difficult.

As the authors pointed out, there are 42, or perhaps more separate agencies trying to deal with separate aspects of this problem. Despite their efforts, the epidemic of accidental death and injury has gained in magnitude and seriousness.

If we are to learn the lessons of history, we would do well to look at the experience of agencies concerned with cardiovascular disease and cancer. In both of these cases, really effective, broadly-based action was delayed pending the launching of an educated campaign by an aroused public. The American Heart Association and the American Cancer Society were both extremely influential in the arousal and education of the public. At present, these two societies alone have a combined budget of close to one hundred fifty million dollars per year and can put an army of many thousands of volunteers into the field. Because of the massive public support and through the influence of a few powerful political, business, and professional figures, the millions of dollars of support donated by the citizens of this country have been expanded by federal and foundation support to attack the problems of cancer and vascular disease through research, education of the public, and key service efforts. If a physician wishes to obtain transportation for a cancer victim, for instance, he can, in almost any major city in the country, merely call the Cancer Society and the transportation will be provided. Obviously, there is no counterpart for trauma, despite the fact that it is the third major killer and probably the major disabler of young, productive people in this country.

Because of this lack, the National Research Council, in 1966, recommended the formation of an American Trauma Society to offer a "global" interest in the problems of trauma and to organize and arouse public response through the three basic avenues of service, education, and research. The American Trauma Society, with national head-

quarters in Hershey, Pennsylvania, is now three years old, and, with the generous support of the American Cancer Society and the American Heart Association, has over 1,500 founding members across the country, and now has nine organized state divisions, including California, with many other states in the process of forming divisions. There are over 120 founding members in California, and we would like to increase this number manyfold. Anyone interested in further information may contact the undersigned.

THOMAS K. HUNT, MD
San Francisco

Rigid Tube Bronchoscopy

TO THE EDITOR: In your November 1973 issue there is a summary on fiberoptic bronchoscopy by Lowell E. Renz. [Renz LE: Fiberoptic bronchoscopy, *In* Important advances in clinical medicine —Chest diseases. Calif Med 119:42-43, Nov 1973] I agree with Dr. Renz that the development of flexible fiberoscopy is an important one and there is no question that the art and science of flexible fiberscopes of all types will increase over the years.

However, I object completely to his observation that the hazards and risks of performing a rigid tube bronchoscopy frequently outweigh the benefits when applied in respiratory failure. This is simply not so and I think it is a disservice to suggest to younger physicians and surgeons that rigid tube bronchoscopy is outmoded. I have been using the rigid tube for nearly forty years and I have bronchoscoped innumerable people with respiratory failure and with postoperative atelectasis without any complications insofar as use of the rigid tube is concerned. Continuous ventilation is, of course, possible with the rigid tube. By and large, therapeutic bronchoscopy and particularly aspiration is much better accomplished by the rigid tube than it is by the flexible fiberscope. It has been standard procedure for years to use a rigid tube in a patient's room, or in intensive care and I have never seen any ill effects from it. I think it is high time that we recognize the advantages and the benefits of the flexible fiberoptic bronchoscope, realizing at the same time that these benefits should be placed in proper prospective to the uses of the rigid tube.

PAUL C. SAMSON, MD
Oakland

* * *

The Author Replies

My article did not state that rigid bronchoscopy has been outmoded. It was not intended to be an in-depth discussion of the pros and cons of rigid versus flexible fiberoptic bronchoscopy. It was intended to be a brief description of the instrument and short résumé of the uses of the flexible fiberoptic bronchoscope.

The term *respiratory failure* was intended to identify those patients with decompensated chronic obstructive pulmonary disease. Many of these patients require intubation and ventilatory assistance. Removal of the endotracheal tube and immediate insertion of rigid bronchoscope requires general anesthesia and/or muscle relaxants. General anesthesia in the hypoxic or acidotic patient represents increased liability for cardiovascular complications. Although ventilating rigid bronchoscopes have been available for many years, it was recently pointed out that certain techniques and types of ventilating bronchoscopes were insufficient in maintaining alveolar ventilation.[1] This was reflected in progressive respiratory acidosis. The bronchofiberscope does not require general anesthesia or paralyzing muscle agents since it can be utilized through an endotracheal tube while maintaining adequate, uninterrupted ventilatory assistance.

LOWELL E. RENZ, MD
Carmichael, California

REFERENCE

1. Morales G, Epstein B, Cinco B, et al: Ventilation during general anesthesia for bronchoscopy. J Thorac Cardiovasc Surg 57:873, Jun 1969

Trauma Rounds

Chief Discussant
LYNN F. BAKER, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is the first of a series of Conferences on Trauma at San Francisco General Hospital.

Refer to: Baker L: Penetrating abdominal wounds (Trauma Rounds). West J Med 120:252-254, Mar 1974

Penetrating Abdominal Wounds

DR. CHARLES GLASSMAN:* A thirty-year-old man was first seen in the Emergency Room 11 November 1973 with gunshot wounds to the abdomen. On admission the patient was unresponsive, in severe shock with poor peripheral perfusion and was unable to give any history although he did make purposeful movements. The blood pressure was unobtainable and the pulse was 120 per minute and thready. After immediate resuscitation with three liters of balanced salt solution the blood pressure became palpable at 110 and the pulse was 100.

There were two bullet wounds in the abdomen, one just to the left of the umbilicus and one over the left iliac crest. An abdominal x-ray film was negative for bullet fragments or missiles. A film of the chest was clear. The admission hematocrit was 40 percent. Urinalysis showed 4+ red blood cells. An intravenous pyelogram did not show any extravasation of dye from the bladder or the upper urinary tract. Laparotomy was promptly carried out.

DR. DONALD TRUNKEY: *Doctor Gadacz, would you like to discuss what you found at operation?*

DR. TOM GADACZ:† At the time of laparotomy, there was some blood in the peritoneal cavity which appeared to be coming from the right lower quadrant. This area was packed so as to control what appeared to be venous hemorrhage. On further abdominal exploration considerable soilage of the peritoneal cavity from small bowel contents was observed. There were ten separate entrance and exit wounds in the small bowel and a 3 cm tangential wound of the cecum. These were quickly closed with Allis clamps, and attention was again turned to the bleeding site. The gauze packs were gradually removed to expose it. On exploration of this area a tangential injury of the right hypogastric vein at its junction with the common iliac was seen. In order to control a jagged defect, it was felt necessary to ligate the external iliac, internal iliac and the common iliac veins. After the venous bleeding had been controlled, the bowel injuries were treated definitively. The multiple holes in the small bowel were in close proximity and were treated by ileal resection and anastomosis. The cecum was then resected and ileostomy and a right colon mucous fistula performed rather than hazard ileo-colonic anastomosis.

DR. TRUNKEY: *Doctor Fairley, you were the staff anesthesiologist in this case. Do you have any comments about the intra-operative management?*

DR. BARRIE FAIRLEY: The biggest problem we had was keeping up with the volume lost. At one point during the operation, we asked the surgeons

Supported in part by NIH Grant CM 18470.
*Intern.
†Chief Resident Trauma Service.
Reprint requests to: D. D. Trunkey, MD, University of California Service, San Francisco General Hospital, San Francisco, CA 94110.

to stop so that we could catch up with the volume resuscitation.

DR. TRUNKEY: *At what stage during the operation was the problem most acute?*

DR. FAIRLEY: He required a rapid push of volume just before induction of anesthesia. Once the iliac vein injury was packed, we were able to catch up but another critical fall in volume occurred while the surgeons were trying to gain control of the venous bleeding in the pelvis.

DR. BLAISDELL: Everyone forgets that venous bleeding is just as catastrophic as major arterial bleeding. The blood flow in a great vein is identical to that in the corresponding artery. It is easy to be lulled into a sense of security with venous bleeding because it is low pressure and therefore less dramatic. Yet it is often more difficult to handle than arterial bleeding. Dr. Fairley, at what point did you ask the surgeons to desist in the dissection so that you could catch up?

DR. FAIRLEY: As I recall, it was at the time that the systolic blood pressure reached 50.

DR. BLAISDELL: One must remember that, with most venous bleeding, control can be relatively easily achieved by using either packs or direct pressure with sponge sticks directly over the injury. If the condition of the patient is deteriorating, the anesthesiologist should communicate this information to the surgeon who should halt further dissection. Most of these venous injuries are relatively easily controlled temporarily with packs, permitting blood volume to be replaced. This course was followed initially in this case, but it required reinforcement by the anesthesiologist when volume was once again lost during dissection to expose the venous injury. Since great veins often have the consistency of wet tissue paper, control of hemorrhage is best obtained by trapping the area of injury between judiciously placed packs and then gently unrolling the packs so as to expose the area of injury for definitive dissection and repair or ligation.

DR. TRUNKEY: *We have with us today a distinguished visitor from the University of Natal, Durban, South Africa, Dr. Lynn F. Baker, who is Professor and Chairman of the Department of Surgery. Dr. Baker, you have had considerable experience with trauma in your environment; would you mind commenting on this case please.*

DR. BAKER: We were not provided any information about this patient's postoperative course. I have followed him and I have been impressed with the benign postoperative course in respect to his intestinal injury. The ileostomy is functioning normally and he appears well. There is tenderness over the common femoral and the superficial femoral vein, but minimal tenderness in the popliteal fossa. It would be difficult to criticize the management of this patient, for he has done so well. Generally, if there are isolated perforations at the small bowel without extensive local injury and the blood supply is good, I would favor closure of the perforations with an inverting suture. When the damage is more extensive, then resection with primary small bowel anastomosis is the treatment of choice. I would support the decision to resect the two areas of bowel that were extensively damaged rather than try to close multiple holes with possible compromise of intestinal viability.

The only possible point in the management with which I may take exception is that of ileostomy and mucous fistula; and I wonder if the patient could not have been as well served with a primary ileum-to-right-colon anastomosis. I would think this would be dependent on how much damage there was at the time of laparotomy and how much contamination of the peritoneal cavity. If there was pronounced contamination, then I think the ileostomy is acceptable treatment. I think I would have done an ileocolostomy with drainage, but I do think that this is open for comment.

DR. GADACZ: The reason we elected not to do a primary anastomosis is that there was considerable contamination of the peritoneal cavity combined with major vascular injury, shock and multiple transfusions. Another reason was the presence of a large mesenteric and retroperitoneal hematoma.

DR. BAKER: *What was the interval of time between injury and treatment?*

DR. GADACZ: We do not have information about that, but considering the time of day, it should not have been more than 30 minutes. It took another 30 to 45 minutes to prepare the patient and induce anesthesia.

DR. BAKER: What troubles me about colon injuries is that large bowel is "bad bowel" and it deserves the respect that it received in this particular case. Because of the short period between

injury and operation I do believe that I probably would have done a primary ileocolostomy, and that is the only thing I would differ with in the treatment of this case.

DR. BLAISDELL: We cannot knock success, and the conservative approach in this patient has certainly paid off very well. However, I believe that I would side with Dr. Baker in this case. There is a certain morbidity associated with take-down of the ileostomy at a second operation. Assuming that the interval of time between injury and treatment in this case was 45 to 60 minutes, then the contamination was relatively superficial and good peritoneal toilet should have been possible. A primary anastomosis of the small and large bowel should have healed well and would have avoided a second operation and its associated morbidity. If there is any doubt, however, it is far better to avoid an anastomosis in a contaminated field, particularly in the presence of shock and associated trauma. The other consideration is the associated trauma that took place in this injury, and the unknown factor in this was the type of missile and its relative velocity. Doctor Thomas Hunt has shown that remote trauma alone can interfere with wound healing. This is associated with decreased oxygen tension and increased collagenase activity. For this reason, the greater the magnitude of overall injury, the greater the possibility that bowel anastomosis will not heal, and the more conservative the management should be.

A PHYSICIAN: *Doctor Baker, would you comment on the management of transverse and left colon injuries in general?*

DR. BAKER: I think these are more difficult to manage because of the vascularity and the nature of the bowel content. These are best managed by proximal diversion of the fecal contents by colostomy or by exteriorization of the injured area.

A PHYSICIAN: *Do you ever think there is an indication to primarily close a left colon injury?*

DR. BAKER: Yes, I suppose so. If it's a stab wound with solid content within the colon, minimal contamination and negligible damage to the bowel wall, it might be judged safe to carry out primary closure. In any event, I would not omit to drain the injury and if there were any doubts at all I would exteriorize the injured bowel. My view would be that if in doubt the bowel is better out of the abdomen.

DR. TRUNKEY: We might summarize the management in this case by concluding that when there is simultaneous vascular and gastrointestinal injury, immediate attention must be given to the vascular injury and hemorrhage must be controlled before anything else is done. Once bleeding is temporarily controlled, volume should be restored before an attempt is made to treat the vascular injury definitively. Small intestinal injury can be treated by simple closure of any perforation or resection, if multiple areas of injury occur in close proximity. Right colon injuries usually require resection with either primary ileocolic anastomosis or exteriorization of the divided bowel ends, depending on the length and degree of contamination, and the associated injury. Transverse and left colon injury should be treated by closure and proximal division (colostomy) or by exteriorization.

I wish to thank Dr. Lynn Baker for his critical commentary.

Refer to: Wilson T: University of Oregon Medical School (Medical Schools of the West). West J Med 120:255-262, Mar 1974

University of Oregon Medical School

ONE MARCH MORNING 106 years ago, three students hurried down a board walk on the campus of Willamette University in Salem. They opened a squeaky wooden door and climbed the stairs to their first class. Twenty weeks later at commencement exercises the three graduates received their degrees in medicine.

Medical education had begun in Oregon.

This year the institution, which was born in Salem and took its first steps in a mortgaged grocery store in downtown Portland, has developed into a $90 million, 24-building complex on a 101-acre hilltop campus. And it is still growing.

Following sanction of the 1973 Oregon legislature, the University of Oregon Schools of Medicine, Nursing and Dentistry, all on the UOMS campus, are being merged to form the University of Oregon Health Sciences Center. Search is under way now for a president to head the center. Deans of the three schools will then function under the new president, who will, in turn, report to the State Board of Higher Education.

The story of medical education in Oregon, and the emergence of the University of Oregon Medical School from the backroom or loft days to its present national stature is a colorful page in Far West history.

Early records show only 115 physicians living west of the Cascade Mountains in 1860-1863, with a few others among the gold miners who remained in Oregon following the Civil War. A problem familiar today became painfully evident —not enough reasonably well-trained physicians to meet the needs of a rapidly increasing population. So A. C. Gibbs, then Governor of Oregon, and a group of physicians asked the board of trustees at Willamette University in Salem to establish a medical department in Portland, the largest town in the state. In February, 1865, the board established the "Oregon Medical College" and six men were appointed to the faculty. But the fledgling medical department never materialized.

Credit for the next step goes to Dr. J. H. Wythe, a physician and clergyman as well as president of Willamette University, who decided his school should try again in Salem. A committee was named to discuss the inactive medical department in Portland and the committee's proposal was adopted in November, 1866. Six men, the first faculty to give medical instruction in the Northwest, were elected.

The first course of lectures began March 3, 1867, and at commencement the same year the first three graduates, W. A. Cusick, D. M. Jones and J. L. Martin, received degrees in medicine.

The Willamette Medical Department was the third of its kind west of the Mississippi and the first western medical school north of San Francisco.

The faculty's ambition to develop a "first class school" was in keeping with the missionary mo-

Reprint requests to: Public Affairs Office, University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland, OR 97201.

The University of Oregon Medical School today. Building in lower right foreground is Child Development and Rehabilitation Center, nationally recognized for its functional architectural design. Center structure is 14-story teaching hospital, flanked in background by central campus complex.

tives which founded Willamette in 1842, but their purpose was in no way as difficult as it would be today. Laboratories were practically unknown and the elaborate clinics and dispensaries then to be found in European medical centers were as foreign as the Sphinx. The requirements were simple: some chairs and possibly a blackboard for the lecture room and any kind of enclosed space where a few cadavers could be dissected.

Although equipment was no particular problem, people soon were.

There is something in the nature of most physicians that makes them extremely independent creatures, inclined to shy away from controls. Because there was no firm administrative policy established between Willamette and the medical faculty, the physicians preferred to govern themselves without bothering to consult the board of trustees. And they did. The doctors also found many areas of disagreement within their own ranks.

In spite of the controversies, the school continued to operate and in 1876, 23 students were registered. Then, perhaps because of continued dissension, the board of trustees gave unanimous approval to a medical faculty recommendation to remove the department to Portland. A new faculty was named, including several men who had been with the Salem Medical Department.

At the first faculty meeting in Portland, held in June 1878, rooms were rented above a livery stable. The first formal instruction took place the following December, and the Portland population of 19,128 certainly offered greater clinical facilities than Salem.

Impetus from Formation of Oregon State Medical Society

Still another factor which influenced the move was the organization four years earlier (1874) of the Oregon State Medical Society. At the society's first meeting a committee on medical education was appointed to report on the medical institutions in Oregon, instruction offered, requirements

for graduation, methods of examination and the number of pupils and graduates at each commencement.

Formation of the state medical society gave physicians in the state a means to express their interest in medical education. In fact, at the society's fifth annual meeting a special committee was appointed to attempt an examination of the medical department of Willamette University.

A significant proposal was made and adopted unanimously at the society's meeting in 1880: that the society prepare a proposal stressing the importance of "a high standard of graduation and that higher preliminary attainment be required of all applications for admission." It was probably boosted along by a state medical society report in 1879 which read: "In this connection we take occasion to protest against the prostitution of the title M.D. so commonly practiced. . . . The right to be called 'doctor' is possessed only by those who have that degree legally conferred upon them. . . . The ignorant pretenders who brazenly put 'M.D.' to their names to sell 'sody,' 'sweat oil' and 'blew mas' in their prescriptions, who cannot tell mumps from erysipelas . . . such pretenders we say do us but little injury for their ignorance is so apparent that the public is not long in perceiving it. . . . "

In 1879 a man who was to play a vital role in medical education in Oregon joined the Willamette Medical faculty as lecturer on diseases of the mind. He was Dr. Simeon E. Josephi, a graduate of Toland Medical School in San Francisco, who had taken up residence in east Portland. In 1880 when Willamette was admitted to membership in the Association of American Medical Colleges, Dr. Josephi was also given the chair of anatomy.

The school outgrew its quarters above the livery stable and in 1885 a new structure was built in what was then the heart of the city. Behind its Victorian embellishments it contained a 150-seat auditorium, a dissecting room with 20 tables and a new refrigerator large enough to store 30 bodies for dissecting material. This building housed the school until the move back to Salem in 1895.

Progress in medical education was slow, as it was across the country, until Johns Hopkins University School of Medicine opened in 1893. This was the first school in America to require a bachelor's degree for admission.

But in a brief 20 years Oregon's wilderness physicians had pushed and prodded, fought and labored, defied Indians, epidemics, and ignorance, to establish and support a medical school with standards comparable to many in the far older eastern cities.

In 1883 attendance requirements were moved up from two to three courses of lectures to qualify a student for medical examinations.

Clinics were held in all the "practical branches," and at the end of the second year final examinations were given in anatomy, physiology and chemistry, but attendance at lectures in these subjects was still required during the third year. The last year included surgery, theory and practice of medicine, materia medica and therapeutics, obstetrics and gynecology and special branches, together with the clinics. This change marked the beginning of a graded curriculum such as was established at Northwestern University Medical School, then the Chicago Medical College, in 1878.

During the next 12 years two events affected the progress of medical education in Oregon. One was moving the Willamette Medical Department back to Salem in 1895. The immediate cause, according to the Willamette board of trustees' minutes of October, 1895, was the "sudden withdrawal of all hospital facilities" in Portland. This apparently referred to the old Methodist Hospital that was closed after scathing attacks against it in the local papers.

Lacking other facilities, the medical faculty appealed to the board of trustees for aid. Appalled at wasting 17 years of effort, they bustled about to provide more or less temporary quarters for the uprooted medical department at Salem, where the school reopened and functioned until a new brick building was erected for medical instruction on the Willamette campus in 1905.

"New and Modern" in an Unfinished Loft

It was described in the Willamette University catalog as "new and modern in every detail" but this statement apparently employed some literary license. The dissecting room was located in an unfinished top floor of the building in a bare area with exposed rafters and studding. Some tables for cadavers were provided, but there was no modern equipment for an anatomic laboratory. The medical department occupied this building until 1913 when it was discontinued by a merger with the University of Oregon Medical School.

In 1887 a significant event occurred, a split in

the Willamette Medical Department faculty which led to the formation of the University of Oregon Medical School.

The trouble began over a new appointment to the chair of obstetrics. At a faculty meeting a motion was made that "gave rise to a protracted and acrimonious discussion during which much personal bitterness was manifested and an apparently irreparable breach created in the faculty." When the meeting was ended, the entire faculty had resigned and the recording secretary was instructed to strike out most of the minutes.

Even after tempers cooled four men remained adamant, and a month later a letter to Willamette's acting dean made their resignations official. The dissenters were Drs. K. A. J. Mackenzie, H. C. Wilson, George M. Welles, and S. E. Josephi. They were joined by several other local practitioners and together set about organizing a rival school.

One of the most active men in the project was Dr. C. C. Strong, a brother-in-law of Judge M. C. Deady who was then president of the board of regents of the state university. The judge's interest in the new venture may have had some influence on the regents, who granted a charter in the name of the University of Oregon Medical School.

Financed by a Note Signed by the Faculty

At a June meeting in 1887, four other physicians joined the first four rebels to be named professors in the original charter. It specified that "the course of study in said school of medicine preparatory to graduation therefrom shall embrace two years."

Dr. Josephi was elected dean and instruction began in the fall of 1887 in a former grocery store which was moved to a sliver of land on the Good Samaritan Hospital grounds at what is now 23rd and Marshall streets in Portland. The building contained a lecture room on the ground floor and a dissecting room above. Cadavers were hauled up through a trap door in the floor with a block and tackle.

The venture was financed by a $1,000 loan from the First National Bank of Portland, on a joint note signed by the faculty members. When Marshall Street was extended in 1889, the little building was moved, then moved again in 1893 to make room for the "sightly, compact and well-equipped medical college building" erected that year. As the school was close to both Good Samaritan and St. Vincent's hospitals, surgical and

University of Oregon Medical School's second location was in northwest Portland.

medical patients were available for observation under treatment and the new structure served the school well until 1919. Then, even as equipment was being moved to the Medical Science building on the present campus, it burned.

The fire did have certain benefits. It is reported to have provided a handy way to dispose of some pink-striped laboratory coats that Dr. William (Pop) Allen had bought. During the excitement a young laboratory assistant rushed heroically into the burning building, grabbed all the coats and threw them into the flames. Rumor persists that he was awarded a medal, for taste as much as for valor.

The first admission requirements in the new quarters were "satisfactory evidence of knowledge of the common English branches including reading, writing, spelling, grammar, geography, arithmetic and so forth." A minimum of three years was required for graduation.

Although some time had been given to teaching microscopy, histology and physiology, the first actual laboratory course in bacteriology was given in 1892 by Dr. A. E. Mackay, who proudly displayed the first tuberculosis bacillus seen under a microscope in the Pacific Northwest. By 1898, when the school adopted the requirements of the American Association of Medical Colleges, the course had been lengthened to four years and studies were being graded.

The late Dr. Laurence Selling recalled: "The lecture room was located on the main floor and there were cuspidors scattered around through it,

Army National Guard helicopters transport critically ill newborn babies from remote areas of Oregon to UOMS Neonatal Intensive Care Unit. Pediatrician and nurse accompany plane.

since so many of the boys chewed tobacco. The anatomy lab was located on the second floor where there was a side door which was the one most used. In the summer time it was as natural as breathing when coming out to look up to see if the water bag was coming down. In fact, during the summer session, the sidewalk was kept wet with this favorite pastime. The winter season didn't dampen the spirit much either."

The Spur of the Flexner Report

But the days of lighthearted antics were running out, for too many graduates were being failed by the State Board of Medical Examiners. Both the school and faculty were under attack by the press, and the situation became so acute that it was taken up by medical societies and local journals.

The *Medical Sentinel* commented: "Either the medical colleges of Oregon ought to improve or disband or else there should be a change on the State Examining Board by the removal of one or more members."

At the 1907 examinations, five of the eight graduates who appeared failed to receive a license to practice. Apparently much of the difficulty could be laid to the different standards held by members of the State Board.

Apparently some officials, with the best of intentions, were attempting to meet the pace set by the American Association of Medical Colleges and the American Medical Association—a pace so fast that the faculty found it almost impossible to follow at that time. Smarting under criticism at home and from the AAMC, they voted in November, 1907, to resign from the association, rather than be ousted.

But the school's troubles were just beginning, for in 1910 it was the object of a bitter denunciation in the famous report of Abraham Flexner on Medical Education in the United States. For a time it appeared the institution would go under, as many others had. In 1906 there were 161 medical schools in the country, but not more than 80 had any stature, according to the American Medical Association report by the Council on Medical Education and Hospitals.

Demands for equipment and salaries for full-time instructors in at least the laboratory subjects soon weeded out many of the weaker schools, and before long only 135 remained. Of these, 29 were rated as Class B and 72 as Class A. The University of Oregon Medical Department rated an A.

The *Medical Sentinel* rejoiced: "It places the Oregon School in the same classification as the big medical schools in the East."

Lacking financial support to meet the insistent demands for higher standards, the Portland school had increasing difficulty. At this time the budget from the state's general fund was $1,000 annually. Needing money for equipment, for full-time instructors, for all purposes, the faculty appealed to the board of regents of the state university. As a result the appropriation was increased to $2,500 yearly and the president of the board recommended increasing this amount to at least $10,000 annually so that the school could meet the requirements for continued recognition by the standard-setting authorities.

At its next session the legislature came to the rescue with an appropriation of $30,000 for the 1911-1912 biennium. Bolstered by the promise of more support, the faculty took another forward step, the appointment of Dr. David N. Roberg as the first full-time instructor at the school.

Higher standards brought increased need for better hospital and dispensary facilities for the students, and in 1909 preliminary arrangements were made to use the Multnomah County Hospital for teaching purposes. By 1913, six salaried instructors had been added to the staff.

After guiding the school through its first critical 25 years the first dean, Dr. Simeon Josephi, resigned in 1912 to be succeeded by Dr. K. A. J. Mackenzie. The following year the Willamette Medical Department in Salem was consolidated with the Portland school.

A Hilltop Campus

With each class, pressure increased for larger laboratories, better equipment, and modern instruction. No one was more aware of the need than Dean Mackenzie. Fortunately, he had been chief surgeon for the Oregon Railway and Navigation Company and knew members of the company's board of directors well. Some years before, the company had bought a piece of land, sight unseen, for its river frontage. The site extended to an almost inaccessible hilltop a mile and a half up-river from the city. But Dean Mackenzie saw the location through different eyes. He visioned a medical center away from the city's noise and grime and he lived to see his dream begin to become a reality. He persuaded the railroad officials to donate 20 acres atop Marquam Hill for the school, and from that day he worked unceasingly to develop "Mackenzie's Folly" as some called it. The gift of a new campus in 1914 was followed the next year by a legislative appropriation of $50,000 for a new building.

The cornerstone of the first unit, the Medical Science Building, was laid May 1, 1918, and the three-story building was completed the following year.

In the meantime the need for a new county hospital had become urgent. Knowing clinical facilities adjacent to the school would be valuable to the students, Dean Mackenzie offered the Multnomah County commissioners nine acres for a county hospital and a nurses' dormitory. His offer was accepted and construction of Multnomah Hospital was well under way in 1920 when the dean was fatally stricken with angina pectoris. (The original county hospital, with its supplemental wings, was this year purchased by the Oregon legislature for the medical school's teaching and patient care program. Operating costs of the institution were formerly absorbed by the county, although the medical school faculty has always staffed the 334-bed hospital.)

During the school's formative years and those that were to follow, the honor roll of men who aided medical education in Oregon grew impossibly long to recount. High on this roster is the name of Dr. Richard B. Dillehunt, third dean of the medical school and chief surgeon of the Shriners' Hospital for Crippled Children for 19 years. Although he had been assistant dean a major share of the time since 1912, his election took place only after an intensive battle between two factions of the faculty. The majority of the older clinical members considered the laboratory sciences as merely a necessary adjunct for training physicians. The younger clinical men and the laboratory staff believed equally strongly that medical education must be primarily a science. Dean Dillehunt was destined to walk a tightrope between the two factions until each recognized the importance of the other's role.

A New Gift of Land

In 1924 the campus was enlarged by a gift of 88 acres of adjacent land from the Jackson family, publishers of the *Oregon Journal*. The tract provided room for future construction, and 25 acres of it were deeded to the United States Government in 1926 as a site for a veterans' hospital.

The school now entered a period of consistent growth. In 1926 Doernbecher Memorial Hospital for Children was completed, providing 70 beds for sick and disabled youngsters.

In 1931, $400,000 from the General Education Board of New York provided the medical school with a modern outpatient clinic on the campus. In 1939 the University State Tuberculosis Hospital was completed with state and federal funds as well as gifts from the family of former Governor Julius L. Meier.

During the same year the Medical School Library and Auditorium were completed with a gift of $100,000 from Dr. John E. Weeks, a like amount from the Rockefeller Foundation and a grant of $163,500 from federal funds.

The handsome structure was the realization of a long-cherished dream for medical librarian Bertha Hallam. She had arranged the school's first collection of books in an elevator shaft back in 1919 and she prodded the library's growth with indomitable determination up to and even beyond her retirement in 1965.

The library is now a major source of postgraduate education for physicians. Throughout the years books, periodicals, historical items, and gift funds have arrived in a steady stream; and to this day donations from the medical societies are given annually.

In 1941, Dean Dillehunt established a division

of experimental medicine at the school, headed by Dr. Edwin Osgood. This first formal step into the medical unknown opened a path which would one day take Dr. Osgood to international eminence for his work in leukemia and chromosome research.

In 1941, Pearl Harbor shattered many a plan, personal and professional. The faculty was stripped to a skeleton crew as man after man entered military service and those who remained shouldered heavy schedules to support the school's teaching and patient care programs. Instruction was stepped up to a year around schedule to supply physicians for military service as well as for a civilian population that had lost so many of its practitioners to the needs of war. As people by the thousands poured in to work in Oregon war industries, the demands upon physicians were so great that many of them became casualties of war from sheer overwork.

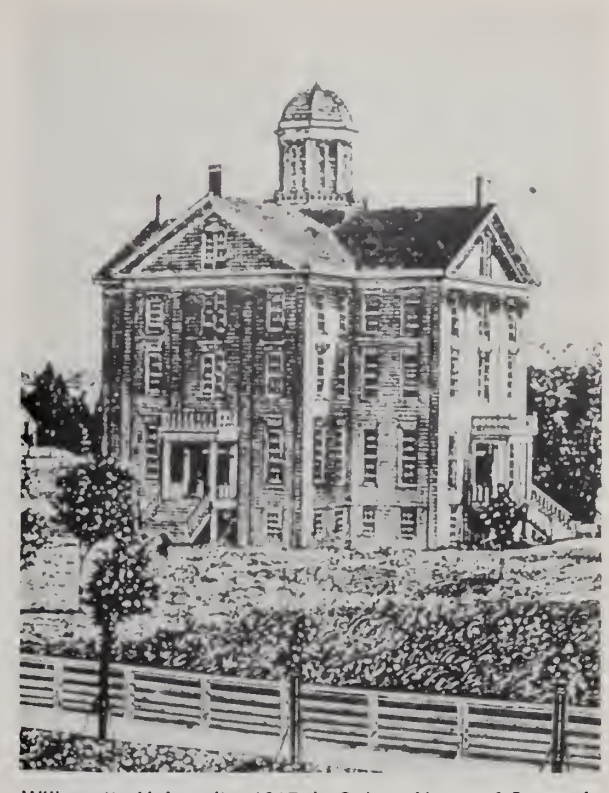
In 1943 a series of heart attacks forced Dean Dillehunt into semi-retirement and he remained Dean Emeritus until his death in 1953.

The fourth dean of the medical school was uniquely qualified to fill the post. He knew every step of the way. From the day David W. E. Baird enrolled at the University of Oregon in 1918 through his years as a student, intern, instructor, practicing physician, professor and director, each step was father to the next until all he had learned on the long road up became a Gibraltar of experience and knowledge which supported the medical school until his retirement in 1968. He was succeeded by Dr. Charles N. Holman, the present dean. Having moved from University of Oregon Medical School student to associate dean in orderly progression in the past 42 years, he too has a thorough training for the job. Under his leadership, entering class enrollment has increased from 83 to 114 medical students.

Post-War Education Explosion

The war's end in 1946 brought new dimensions to medical education. During the first 75 years, the school had followed an uphill, often meandering path. Then came explosions of knowledge, each burst illuminating another dark area to be explored.

The schools, the state and county medical societies, various specialty groups—all began offering postgraduate courses and lecture series by visiting scientists. Volunteer faculty members who had long been the backbone of the school's



Willamette University, 1867, in Salem. Home of Oregon's first medical school.

instructional programs returned to teach in record numbers. In 1943 they numbered 102. Today more than 800 men and women practitioners donate their time and skill to some phase of the school's instructional programs.

Each new advance, each new technique kindled more understanding and public enthusiasm for medical education and research. Inevitably, with this support came financial backing at every level of government, as well as from many private sources. State funds built the Crippled Children's Division on the UOMS campus in 1954, and state and federal funds completed the 14-story Medical School Hospital in 1956. It was here that Dr. Albert Starr performed the first successful implantation of an artificial heart valve in 1960. Since that time prosthetic valves have been used to save more than 60,000 lives throughout the world.

In 1962 the nine-story Research Building was completed with $2.5 million from the Oregon State Legislature, the National Institutes of Health and the Medical Research Foundation of Oregon. Now scientists in basic research had a long-overdue home of their own, but characteristically, the building was crowded before the move in had

been completed. The Portland Hearing and Speech Center, an eight-story Women's Residence completed in 1965, projects such as the expansion of the Medical School Library, a seven-story addition to the venerable Outpatient Clinic, the massive Child Development and Rehabilitation Center, a new Basic Science Building, two new parking structures—these, too, symbolize the growth of the medical school.

Postgraduate courses launched by the Kellogg Foundation back in the 1940's have continued to expand as practicing physicians from across the state respond to the need to keep up with the advances of medical knowledge.

This year, as 33 Fellows, 397 medical students, 51 interns and 273 residents continue their education, the medical school campus swarms with young men and women students studying in related fields. The University of Oregon School of Nursing, which began in 1910 with three students, today has 493 in the baccalaureate and 51 in the masters degree programs.

Medical technologists, cytotechnologists, radiologic technologists, dietetic interns, graduate students in the basic sciences and in audiology and speech pathology—all the multiple facets of medical education—bring more than 1,400 students to the campus each year.

In 1943 the full-time faculty numbered 14. This year it is well over 300. In the 1940's annual research grants were less than $75,000. Today they exceed $5,500,000. Teaching programs have been updated, expanded, integrated with laboratory and patient care programs to develop a curriculum geared to today's needs.

An Atmosphere for Progress

An atmosphere of academic freedom has attracted many of the nation's top educators, clinicians and research scientists to the Oregon school, a policy which is paying substantial dividends. The kidney transplant program, for example, has a success rate as high as or higher than any other medical center in the nation, according to statistics from the National Kidney Registry. The transplant surgical team headed by Dr. Russell Lawson has implanted 53 cadaver and 67 related kidneys in the past three years.

The PETS programs (Perinatal Emergency Transport System) which was launched statewide in 1972 is aiding critically-ill newborn babies and women with high risk pregnancies. An air rescue team, developed through the Governor's office and the Oregon Army National Guard, now rushes these endangered patients by helicopter or fixed wing aircraft to the Medical School Hospital. The Neonatal Intensive Care Unit (NICU) headed by Dr. S. Gorham Babson and Dr. John R. Campbell, has achieved an excellent recovery rate for these jeopardized infants. During 1973 the NICU admitted 358 babies, 40 of them via air rescue. Of the total admitted with life-threatening problems, 292 were restored to their parents.

A family practice residency, started in 1971 with three physicians enrolled, now has ten residents. Interest in the specialty has increased since preceptorships with family doctors across the state have been established for medical students, exposing them to the actualities of practice in rural areas. Dr. Laurel Case, head of the division, estimates that 60 to 75 physicians will have completed their training by 1981.

The Faculty Planning Council recently completed a ten-year plan which will increase overall enrollment in health profession vocations by nearly fifty percent. It calls for developing new programs not currently available in Oregon, including training courses for physician's assistants, physical therapists, medical records librarians and occupational therapists. Additional medical residencies scheduled to begin by 1975 include emergency room, oral surgery, pediatric surgery, physical medicine and plastic surgery.

Last year more than 16,000 patients were admitted to the Medical School Hospital and University North and Tuberculosis hospitals. The number of patient visits to the outpatient clinics and diagnostic laboratories exceeded 227,000 and the Crippled Children's Division recorded more than 40,000 visits.

As on-campus patient care, training and research programs move ahead at the Oregon school, continuing education courses for the state's practicing health professionals are keeping pace with expanding needs. The ten-year plan projects a 108 percent increase in enrollment in continuing education courses by 1981.

In summary, the University of Oregon Medical School has, from its humble beginning in a mortgaged grocery store, advanced through the past 86 years to take a well-deserved place among the West's finest institutions dedicated to the training of physicians, nurses and the allied health professionals.

THELMA WILSON
Assistant Director
Public Affairs Office
University of Oregon Medical School

Refer to: McNamara JJ: Early and periodic screening—Medi-Screen program structure and standard setting (Government and Medicine). West J Med 120:263-266, Mar 1974

Early and Periodic Screening

Medi-Screen Program Structure and Standard Setting

JOHN J. McNAMARA, MD, MPH, *Jamaica, New York*

EARLY AND PERIODIC SCREENING, sometimes called Medi-Screen, is a federally mandated health screening program for the Medicaid-eligible population under age 21.

This program has a large potential for introducing change into the medical care system. It also has generated considerable confusion, which may be lessened by a discussion of the program's historical and cenceptual development, the federal guidelines for program structure and the need for standards which will ensure program benefits. Constraints to program success should also be examined. Finally, some implications of this program for health care in general should be drawn out.

The federal guidelines of June 1972 state: "Congress was concerned about the variations from state to state in the rates of children treated for handicapping conditions and health problems that could lead to chronic illness and disability. Senate and House Committee reports emphasized the need for extending outreach efforts to create awareness of existing health care services, to stimulate the use of these services and to make services available so that young people can receive medical care before health problems become chronic and irreversible damage occurs."[1]

This program was established in 1967 by an amendment to the Social Security Act (under nursing home provision in Medicaid). This law provided: "effective July 1, 1969, such early and periodic screening and diagnosis of individuals who are eligible under the plan and are under the age of 21 to ascertain their physical and mental defects, and such health care, treatment and other measures to control or to ameliorate defects and chronic conditions discovered thereby, as may be provided in regulations of the secretary [of HEW]."[2]

The intent of the law is to provide health screening and follow-up services. However, program content was not further defined. Regulations were not published until a lawsuit was filed by the National Welfare Rights Organization.[3] When regulations were issued November 4, 1971, they outlined some issues in the program itself but principally placed limits on the treatment services to be provided in conjunction with this program. However, states were instructed to include in their Early Periodic Screening (EPS) programs: "(1) Establishment of administrative mechanisms to identify available screening and diagnostic facilities . . . to assure that individuals . . . who are eligible . . . receive the services, (2) identification

The author is Director of Community Medicine and Ambulatory Care, Queens Hospital Center Affiliation, Long Island Jewish-Hillside Medical Center. Formerly he was Chief of Children and Youth Unit, Bureau of Maternal and Child Health, California State Department of Public Health.

Reprint requests to: J. J. McNamara, MD, MPH, Director, Community Medicine and Ambulatory Care, Queens Hospital Center Affiliation, Long Island Jewish-Hillside Medical Center, 82-68 164th Street, Jamaica, NY 11432.

of those in need of services furnished by Title V (Social Security Act) Grantees, (3) assurance of maximum utilization of existing screening services."[4] Regulations do identify public sector services such as Maternal and Child Health and Crippled Children Services as major providers. It is assumed that screening services already exist for the child age group, and that only an outreach component, or the way to bring these services and the children together, is lacking.

Although the Kaiser-Permanente system[5] has addressed the question of multiphasic screening in children, aside from the very different model provided in the private practitioner's office and the well child conference, little formal health screening for children exists. It should be noted that the traditional well child conference is designed to provide preventive health services such as immunizations, nutritional advice, and ongoing monitoring of growth and development. An educational thrust is of prime importance. In some settings health assessment by physical examination and screening with laboratory tests is not done. The well child conference also provides a one-to-one interaction between mother and health professional. In many settings the physician is directly involved.

This one-to-one interaction is not the model envisioned in Medi-Screen. The guidelines most nearly resemble the multiphasic screening model. Often the primary purpose of such screening is to establish the health status of a population group as a first step toward improving their level of health. Determining health status and detecting abnormalities *may* lead to diagnosis and treatment and may prevent the progression of illness.[6] However, direct responsibility for the health care of populations, except in limited contexts, does not exist. The problem of evaluation and follow-up after the health data are collected is the major challenge facing a program such as Medi-Screen. In their fully developed, automated and computerized form "mass screening programs essentially may require the reorganization of medical practice and the delivery of health services to the population."[7]

More extensive federal guidelines were issued in June 1972, delineating program scope and procedure in EPS. A minimal screening program must include, the regulations stated, "a health and developmental history (physical and mental), an assessment of physical growth, developmental assessment, inspection for obvious physical defects, ear, nose, mouth and throat inspection (including inspection of teeth and gums), screening tests for cardiac abnormalities, anemia, sickle cell trait, lead poisoning, tuberculosis, diabetes infections and other urinary tract conditions and an assessment of nutritional status and immunization status."[8] Clearly this represents a minimum assessment of health status. Many important health problems will not be detected by this limited approach.

In line with the multiphasic model, the screening process itself is defined as "quick simple procedures carried out among groups of people to sort apparently well persons from those who have disease." The instructions under the definition state: "Although screening should be performed under the supervision of a physician . . . the carrying out of interviews, observations and tests that can constitute the screening process may not require their presence during screening. Nurses, trained health aides, laboratory technicians and trained volunteers can conduct the screening activity. Screening . . . is intended to be carried out with large groups of individuals . . . and is not generally a service provided on a one-to-one basis."[9]

Out of this concept of screening arise two major issues which determine the shape of developing programs and also present major obstacles to program development. They are:

1. Screening is to be provided by paramedical personnel.
2. Screening is viewed as a mass process.

Provision of this screening service by paramedical personnel assumes that these personnel are available and are legally permitted to perform this service.

In California, for example, availability of adequately trained personnel is problematic. It is assumed in the federal guidelines that nurses can perform all tasks indicated in the basic program without further training. In reality, however, nurses have little or no formal preparation in the physical inspection of children or in developmental testing. Extended role nurses or nurse practitioners are extremely limited in number. As of July 1972, there were five educational institutions preparing pediatric nurse associates in the State of California. Programs are not fully operational, but have a maximum capacity of around 80 grad-

uates a year. They have actually graduated 119 nurses from these programs to date. A study[10] in 1971 identified 256 nurses statewide who were actually taking responsibility in the extended role. Many of these had been prepared by on-job training. It is estimated, however, that 1.2 million children and youths are eligible for this screening program in California. There are too few nurses and other personnel, such as physician's assistants, for the job, and many of those who are available cannot be considered instantly qualified to fit into the screening role, especially in the child age group.

There are questions also about the legal status of the extended role nurse and the nurse practitioner that remain unanswered. For example, in California no licensing beyond the Nursing Practice Act exists. This severely limits the kinds of activity that can be performed and the supervision required. For example, independent administration of immunizations is not permitted.[11] The status of physician's assistants has been qualified by Articles 15 and 18 of the Business and Professions Code 1970, which defines the physician's assistant and the content of his training. While such personnel are permitted to take a history and carry out physical examinations, the major use of these workers seems to be in the care of adult patients. Although approved training programs do include concepts of growth and development, training in developmental testing is not included. If physician's assistants are to deal with children, formal training for the purpose will be required.

As the first national health program designed to be delivered by paramedical personnel, EPS creates a situation which will force boards of medical examiners and other licensing bodies to address the questions of task analysis in medical care, requirements for the supervision and control of the quality of services delivered by paramedical personnel, and finally the licensing issue itself.

After legal issues become settled, a strong impetus to the development of training programs can be expected. In the interim, it is imperative that the EPS program be instituted by competent, carefully supervised personnel. To ensure this, rigorous standards must be used in defining personnel qualifications for the program. The California Bureau of Maternal and Child Health has developed tentative equivalency standards based on actual tasks to be performed in the screening process. These are in conformity with the joint statement of the American Nurses Association and the American Academy of Pediatrics.[12] However, equivalency should only be considered as a stop-gap measure until training can be provided through the usual educational channels.

The scope of the program should determine the technical requirements for personnel. Unfortunately, the federal guidelines fail to recognize all the implications of providing this service by paramedical personnel.

For example, with respect to developmental screening, federal guidelines state: "Information from the parent or other person who has knowledge of the child's development, observation of the child, and talking with the child can all be useful in assessing the individual's development. A test such as the Denver Developmental Test can also be used for this purpose. This part of the screening procedure should include assessment of eye-hand coordination, gross motor function (walking, hopping, climbing), fine motor skills (use of hands and fingers), speech development, self-help skills (dressing, eating, personal care) and behavioral development."[13] This guide appears to approve paramedical personnel's use of both an informal developmental assessment with norms of development and a formal testing method which can be scored and used directly as a basis for referral. Yet it would seem unlikely that paramedical personnel would develop clinical judgment to the point that major over-referral would not become a problem, if the informal approach were selected in a given program. For this reason, personnel standards and program content must be closely coordinated.

Standards for the *process* of screening itself need to be established. In setting the standards, priority should be given to determining whether the screening process is capable of identifying conditions and defects. The question of what is an acceptable level of false positive and false negative in such a program needs to be faced. Quality control measures such as on-site inspection and the surreptitious introduction of persons with known conditions into the screening process to test its effectiveness should be considered.

Program standards must also give attention to mechanisms for appropriate referral and follow-up. Professional societies must be consulted. Such a program requires the medical profession to examine its responsibility toward a given popula-

tion. There is nothing in this program that directly affects traditional patterns of delivering curative medical care. However, linkages to the screening system need to be established, and mechanism for follow-up formalized. Direct sponsorship of such a screening program by medical societies might be a most effective way to accomplish this.

Professional involvement, at more than the individual level, is also critical because screening is defined as a mass process in which physicians are not directly involved. This immediately raises the question of responsibility for the patient.

Clearly, responsibility does not rest directly on the paramedical personnel who perform this service. An organizational responsibility is incurred through screening for follow-up. On this point, federal guidelines are contradictory. They state: "To assure that the individual receives necessary treatment, the medical assistance unit should be informed of the recommendations resulting from the diagnostic study."[14] This attempt to shift responsibility for follow-up to a second party, namely, the local welfare office, seems unlikely to produce the expected result, given usual welfare caseloads and priorities. Also, it negates a traditional responsibility assumed by the first contact source of medical care.

Other issues, such as patients' waiting time, minimum level of efficiency and ensuring physical privacy, should be dealt with by setting standards for such items. Since such matters often determine utilization, concern with them should be reflected in specific instructions.

Finally, an outreach component is mandated in the program and is a necessary corollary of the goal of reaching the high-risk population. Standards defining ethical outreach need to be established. To preserve patient free choice, outreach and screening programs designed to direct patients into single established channels of referral need to be controlled. Inducements and pressure to steer patients to a particular screening center must be prevented.

Finally, the EPS program can be little more than a public relations gesture unless it has adequate funding and offers a realistic payment schedule for those who provide the services.

REFERENCES

1. HEW SRS Regulation Guide MSA-PRG-21. Jun 28, 1972, p 1
2. Social Security Act 1905 (a) 4B 1967
3. NWRO v. Richardson, No. 2091-71 (D.D.C 1971)
4. Fed Register 36:216 Tit. 45 Ch. 11
5. Allen CM, Shinefield HR: Pediatric multiphasic program. Am J Dis Child 118:469-472, Sep 1969
6. Hilleboe: Mass health examination as a public health tool. Geneva WHO (Pub Hlth Pap #45),1971
7. Badgley, Wolfe; Public policy and automated multiphasic health testing and services. Provisional Guidelines for AMHTS 3:DHEW # HAHSN 72-3011, 1972
8. HEW SRS Prog Regulation Guide MSA-PRG-21. Jun 28, 1972, p 4
9. HEW SRS Prog Regulation Guide MSA-PRG-21, Jun 28, 1972, p 3
10. Fakkema L: Report of survey conducted in March and April 1971 of nurses who are taking in increasing responsibility in ambulatory services of children in California. Cal SDPH, MCH (unpublished)
11. Office of the Attorney General: Opinion of Evelle J. Younger #CU 72/187. Feb 15, 1973
12. Guidelines on short term continuing education program for pediatric nurse associates. A Joint Statement of the American Nurses Association and the American Academy of Pediatrics. Jan 1971
13. HEW SRS Prog Regulation Guide MSA-PRG-21. Jun 28, 1972 p 14
14. HEW SRS Prog Regulation Guide MSA-PRG-21. Jun 28, 1972 p 19

Refer to: Stevens DA: Infection control in the hospital—A report on workshop discussions (Notes from Important or Unusual Meetings). West J Med 120:267-269, Mar 1974

Notes from Important or Unusual Meetings

Infection Control in the Hospital

A Report on Workshop Discussions

DAVID A. STEVENS, MD, *San Jose, California*

A MEETING on Infection Control in the Hospital was held September 16-18, 1973, at the conference grounds at Asilomar State Beach, California. Under this general topic everything from operating room design, antibiotic use, and nursery bathing practices to catheter purchasing, administrative power, solid waste disposal and disinfectant efficacy was discussed. The meeting was sponsored by the California Medical Association, California Department of Health, California Hospital Association, California Nurses Association and the American Lung Association, and it was supported by a grant from the U.S. Department of Health, Education, and Welfare. It was coordinated by Lois Shearer, MPH, of the Department of Health, assisted by a committee of physicians and nurses. What follows is a synopsis of the lectures, group discussions and individual meetings.

A unique feature of the workshop was the composition of the groups from the various hospitals represented. The groups included the physician who is chairman of the infection control committee in his hospital, an administrator from that hospital, and the infection control nurse ("nurse epidemiologist" is the title used in some institutions). These trios, largely from hospitals in the Western states, were supplemented by experts from the Center for Disease Control (CDC), Atlanta, and the Pan American Health Organization. The infection control nurse (ICN) clearly emerged as a new force in changing the discipline of hospital infection control. Therefore, considerable attention was directed to this role. In practice, the principle functions of the ICN are education, surveillance, data collection and administrative action under the auspices of the infection committee.

Among the problems faced by infection control teams is the newness of this function as a formal, growing activity in many hospitals. The teams often find themselves immobilized by difficulties in changing traditional and entrenched practices in various hospital domains. Only committees which have interested representatives from many sources, and the support of the administration, have made headway among the existing power relationships. The committees also need the expertise which such an interdisciplinary approach provides, for the subject matter is too vast for the chairman and the ICN to master and keep up with. Departments which various committees had incorporated in their representation included: clinical departments, nursing departments, administration, the clinical laboratories (especially bacteriology), central supply, dietary, employee health, pharmacy, housekeeping, respiratory therapy, and other specialized units as may be applicable. Education is a vital function which many felt preceded surveillance and the institution of new procedures. Otherwise, new programs found themselves expending considerable energy promulgating rules which were then ignored. Moreover, the need for education will only grow as ancillary hospital personnel (paramedics, nurse's

From the Division of Infectious Diseases, Departments of Medicine, Santa Clara Valley Medical Center, San Jose, and Stanford University Medical Center, Stanford.

Reprint requests to: D. A. Stevens, MD, Santa Clara Valley Medical Center, 751 South Bascom Avenue, San Jose, CA 95128.

aides) with less formal training increasingly perform complex tasks formerly performed by nurses and doctors. Added to this need are changing educational requirements for traditional disciplines. An example given by one speaker is that microbiology is no longer a course requirement for nursing students.

Another problem identified is that sometimes a physician may be impatient with measures taken by a hospital for epidemiological reasons to protect patients in general, if they impinge on his management of his patient. Such problems usually develop around questions of isolation. The physician's protectiveness toward his patients may take the form of "You can't do that to my patient." A committee that must criticize, say, Nurse A's handwashing practices or Dr. B's wound infection rate must develop great tact. Moreover, serving on the committee frequently involves significant role conflicts, which were described by the participants. It is sometimes difficult for one physician (the chairman, say) to be critical of another on whom he may depend for referrals or with whom he must relate later in other roles. And the chairman may well recognize that he himself could be the offender the next time around. Participants at the meeting stressed that there is no formal source material on ways to deal with problems of this kind.

Most of the chairmen present at the Asilomar discussions were pathologists, a logical extension of their full-time association with the hospital and their connections with the diagnostic microbiology laboratory, although internists and pediatricians with an interest in infectious diseases often fill this role. Compounding the chairmen's problem was the fact that the job was always a sideline and commonly an unpaid one. Most of those who served in this capacity had difficulty giving the job the time it required.

The ICN's expressed anxieties resulting from their new relationships as nurses *vis-à-vis* physicians. Instead of the traditional subservience, in her new role the nurse may find that her activities in data collection can be regarded as snooping, and her attempts at education may cause resentment. A solution offered was closer affiliation of nurse and chairman as a team.

Communications experts at the meeting analyzed some of the problems discussed, and recommended the separation of knowledge deficiency problems, skill deficiency problems, and attitude problems. They emphasized that committees too often label problems incorrectly, and that proper perception of a problem is the first step toward solution.

Another difficulty faced by infection control workers is a lack of adequate data. By consensus, certain source materials are indispensable. One is *Infection Control in the Hospital,* published by the American Hospital Association and available from them at 840 North Lake Shore Drive, Chicago, 60626. A second is *Isolation Techniques for Use in Hospitals,* a U.S. Public Health Service publication available from the Government Printing Office. Both were last revised in 1970. *Proceedings of the International Conference on Nosocomial Infections,* a result of the conference held at the CDC in 1970, also would be valuable and is available from the American Hospital Association. However, a fault shared by these works with others is that while the recommended courses of action are relatively clear, the reasons for them are not.

Obviously, then, a *referenced* set of recommendations is needed to enable infection control workers to understand why a procedure is advised. Some recommended procedures are based on solid scientific study in the laboratory, some on solid epidemiological observations, and others on educated guesses using sometimes meager evidence or application of general principles. Infection control workers need to distinguish among these, both for their educational functions and to determine the vigor with which each is pursued administratively. Many procedures in the hospital have been shown to be unnecessary (e.g., everyone gowning in the nursery), and others with little proven value are inherited from previous "infection control" activities (e.g., culturing of environmental surfaces).

Another problem is that newly published studies too often are poorly done and lack adequate controls, but are quoted by pharmaceutical detail men in support of a particular product. Good studies unfortunately are dispersed in many different journals, each concerned with a different discipline. The task of finding these articles and keeping up with this literature is a formidable one, and the need for centralizing this kind of information in some form was expressed. This task could be a valuable function for a state department of public health because such a program might operate best at the state level.

Finally, even with clear-cut data, decisions sometimes are made on other grounds. An ex-

ample widely quoted was an administrator who was forced to purchase expensive operating room equipment over the opposition of his infection control committee because a group of orthopedic surgeons threatened to send their patients to another hospital.

Money is an acute problem for many programs which are in need of funds for such activities as adding new positions or remodeling facilities. Such requests are met by emphasis at federal, state and hospital levels on countering the rising costs of hospital care.

The inadequacy of most hospital facilities, resulting from deficiencies in design, was another widely acknowledged problem. Few institutions, for instance, planned proper facilities for respiratory isolation, with the controlled and separated air flow that is now required for new construction. Other institutions are unable to care adequately for patients who require certain types of isolation and simultaneously need intensive care. Their units simply were not planned for this dual function.

Workshop participants represented institutions ranging in size and type from a 45-bed rural hospital owned by a religious order to a 1,500-bed urban county-owned hospital. This juxtaposition of dissimilar facilities was instructive, emphasizing the different problems faced by each, and the need for different approaches to control infection in the hospital environment.

Several questions were discussed but not resolved. When the position of ICN is created, what department should this person be under? Although association with the department of nursing might seem logical, this presents some difficulties regarding the independence of the ICN. If the patient's own physician, despite the infection committee's suggestion, does not see a need for isolating a patient with a potentially communicable problem, who should resolve the conflict? How can a hospital staff be assured that those in responsible positions such as infection control committee chairman or ICN are qualified? Should there be a plan for continuing education? A licensing program?

Overall, it appears that in some quarters increased attention to infection control did not result exclusively from a belated recognition of its need. Rather, it was related to the increased attention being paid to this function by the Joint Commission on Accreditation of Hospitals in their pronouncements and inspections. If the programs which evolve are imaginative and far-ranging, and are not restricted to collection of data which are not reviewed and do not effect change, this stimulus will have been beneficial. However, programs created to paper over a real need will do little to make the hospital a safer place. It was clear, in any case, that interest in hospital infection control is growing, and it will be a subject for increased study.

Another conference at Asilomar on this subject is planned for April 28-May 1, 1974.

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

INFECTIOUS DISEASES OF CHILDREN AND ADULTS—Fifth Edition—Saul Krugman, MD, Professor and Chairman, Department of Pediatrics, New York University School of Medicine, Director of Pediatrics, Bellevue Hospital Center, New York City, Director of Pediatrics, University Hospital, New York City; and Robert Ward, MD, Professor of Pediatrics, University of Southern California School of Medicine, Director of Research, formerly Physician-in-Chief, Children's Hospital, Los Angeles. The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Mo. (63141), 1973. 494 pages, $21.50.

This volume will be welcomed by those who have used the previous four editions, which had been directed to infectious diseases of children but which now also include those of adults. This is not an encyclopedia of infectious diseases but includes most of the things important in this country, perhaps those in which the writers have the most experience and interest. Some valuable chapters have been added: on syphilis, gonorrhea, and an excellent one on tuberculosis at all ages contributed by Edith M. Lincoln and David M. Sewell. Discussion could have been expanded in a few subjects. For example, a somewhat more explicit description of how hepatitis B-virus, which cannot be grown on tissue culture, is utilized as an antigen in serological studies with antibody, a subject on which the authors are outstanding authorities. But, why should mumps meningitis, a usually benign form of aseptic meningitis, be placed alongside post-measles encephalitis as the greatest cause of encephalitis? Why is there so little discussion of gonorrheal ophthalmia of the newborn and its prevention and treatment?

But why carp? The "common diseases of childhood" have become less common in children and occur more frequently in adolescents and adults, and no textbook of medicine or pediatrics covers these diseases so comprehensively. Both authors are extremely adept in the laboratory and on the infectious disease wards, and have succeeded in neatly combining microbial and immunologic findings with clinical features. This well-illustrated book has a delightfully smooth, free-running style. It unquestionably will be the most useful and authoritative volume on the subject, not only for the pediatrician but for the internist and family practitioner.

EDWARD B. SHAW, MD

* * *

RADIOLOGIC EXAMINATION OF THE URINARY TRACT—Howard M. Pollack, MD, Associate Professor of Radiology, Temple University School of Medicine, and Director, Department of Radiology, Episcopal Hospital, Philadelphia. Harper & Row, Publishers, Inc., Medical Department, 2350 Virginia Avenue, Hagerstown, MD (21740), 1972. 164 pages, with 145 illustrations, $8.50.

As is true of many loose-leaf textbooks, individual chapters are so well written and so complete that they make excellent monographs on the subject presented. Such a one is *Radiologic Examination of the Urinary Tract*, by Howard W. Pollack, MD. This is the chapter from the 2nd volume loose-leaf textbook of urology edited by Lester Karafin, MD and Richard Kendall, MD.

As the author notes in his preface, ample space has been devoted to such topics as types of procedures, their indications or contraindications and special views, but there is little or no discussion of the radiographic aspects of specific disease processes except as these entities relate to the uses of individual techniques and procedures. Nevertheless, there are excellent examples of many disease processes and a basic approach to urography that makes this monograph a valuable addition to any urologist's or radiologist's library. The discussion of the physiologic mechanisms and media used in intravenous pyelography are well worth review by the most experienced. This is also true of the discussion of complications of urography and contrast media injections.

There is a diagramatic representation of typical ureteral displacements that is an excellent reference. Pyelorenal backflow is covered and the various types and causes are outlined and discussed. Urethrography, cystography, and seminal vesiculography are briefly but adequately discussed, as are retroperitoneal pneumography, ultra sound and renal cyst aspiration. Renal arteriography is thoroughly discussed, but, as the author prepared us in his preface, there are not enough examples of vessel disease shown. The final section, "Radiation Protection in Urology," is a most fitting ending and one that should be heeded by all urologists and allied personnel working in cystoscopy rooms. It is a basic description of the minimal permissible dose of x-ray and the precautions to be taken to avoid any excess radiation in working with it.

TOM M. FULLENLOVE, MD

* * *

MINIMAL CEREBRAL DYSFUNCTION IN CHILDREN—Edited by Stanley Walzer MD, Assistant Professor of Psychiatry, Harvard Medical School; and Peter H. Wolff, MD, Professor of Psychiatry, Harvard Medical School. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 117 pages, $7.50.

It was not too long ago that all children who did poorly in school were classified as mentally retarded. But it has become evident that there is a group (from 5 to 15 percent of the school population) with a learning disorder, who are at least of average intelligence but who have a central processing dysfunction that is generally called minimal brain dysfunction or minimal cerebral dysfunction.

This book includes a number of papers by authorities in the field of minimal cerebral dysfunction in which clinical and experimental data are presented "that focus both on the issue of brain damage and on the developmental 'end products' of the complex interaction between the biologically handicapped child and his surrounding world." One of the papers deals with asphyxia neonatorum in an animal model. The behavior of the survivors is compared with that observed in children with minimal cerebral dysfunction, resulting in many striking similarities. Several of the papers describe the techniques designed to identify and diagnose the condition, including psychoeducational, ophthalmological, and pediatric neurological studies, and the use of the EEG. There is brief reference to the use of dextroamphetamine and methylphenidate in the hyperkinetic child but there is no description of the educational approach to overcoming the serious learning disorders associated with minimal cerebral dysfunction.

This collection of papers will be of interest to those persons specializing in the diagnosis of children with minimal cerebral dysfunction but will not provide much help to the practitioner looking for specifics in treatment and educational approaches.

PETER COHEN, MD

in memoriam

Dillon, Richard, Los Angeles. Died January 8, 1974 in Los Angeles, aged 60. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1940. Licensed in California in 1940. Doctor Dillon was a member of the Los Angeles County Medical Association.

Hammel, Max Arthur, Santa Barbara. Died January 12, 1974 in Santa Barbara, aged 60. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1936. Licensed in California in 1938. Doctor Hammel was a member of the Santa Barbara County Medical Society.

Handelman, Jack H., Los Angeles. Died January 6, 1974 in Beverly Hills of cerebral vascular accident, aged 66. Graduate of the Ohio State University College of Medicine, Columbus, 1933. Licensed in California in 1948. Doctor Handelman was a member of the Los Angeles County Medical Association.

Keate, Wendell Snow, Santa Monica. Died January 3, 1974 in Los Angeles of acute coronary occlusion, aged 71. Graduate of Rush Medical College, Chicago, 1929. Licensed in California in 1930. Doctor Keate was a member of the Los Angeles County Medical Association.

Lehman, Robert G., San Pedro. Died January 1, 1974 of heart disease, aged 60. Graduate of Hahnemann Medical College and Hospital of Philadelphia, 1938. Licensed in California in 1947. Doctor Lehman was a member of the Los Angeles County Medical Association.

Leik, Donald William, Long Beach. Died December 26, 1973 in Long Beach of heart disease, aged 66. Graduate of State University of Iowa College of Medicine, Iowa City, 1932. Licensed in California in 1946. Doctor Leik was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Levy, Marvin Shephard, Los Angeles. Died December 24, 1973 in Los Angeles of heart disease, aged 59. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1940. Licensed in California in 1945. Doctor Levy was a member of the Los Angeles County Medical Association.

Maddox, Robert C., Antelope Valley. Died January 3, 1974 in Palmdale of heart disease, aged 43. Graduate of the University of California at Los Angeles, School of Medicine, 1960. Licensed in California in 1961. Doctor Maddox was a member of the Los Angeles County Medical Association.

Mollath, August L., Santa Maria. Died December 28, 1973 in Santa Maria, aged 68. Graduate of University of California Medical School, Berkeley-San Francisco, 1930. Licensed in California in 1930. Doctor Mollath was a retired member of the Santa Barbara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Moore, Harold M., Porterville. Died December 15, 1973 in Phoenix of a perforated gastric ulcer, aged 47. Graduate of the University of California at Los Angeles, School of Medicine, 1960. Licensed in California in 1961. Doctor Moore was an associate member of the Tulare County Medical Society.

Morris, David Lawrence, Stockton. Died January 1, 1974 in a boating accident near the mouth of the Calaveras River, aged 38. Graduate of the George Washington University School of Medicine, Washington, DC, 1964. Licensed in California in 1968. Doctor Morris was a member of the San Joaquin County Medical Society.

Neilsen, Melvin L., Petaluma. Died January 10, 1974 in Petaluma of heart disease, aged 71. Graduate of the College of Osteopathic Physicians and Surgeons, 1930. Licensed in California in 1930. M.D. degree from California College of Medicine, 1962. Doctor Neilsen was a member of the Sonoma County Medical Association.

Oakleaf, Donovan Carl, Healdsburg. Died January 3, 1974 in Cloverdale of myocardial infarction, aged 70. Graduate of the University of Colorado School of Medicine, Denver, 1930. Licensed in California in 1930. Doctor Oakleaf was a retired member of the Sonoma County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Person, Edward C., San Diego. Died January 24, 1974 in San Diego, aged 78. Graduate of the University of Nebraska College of Medicine, Omaha, 1926. Licensed in California in 1939. Doctor Person was a retired member of the San Diego County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Rook, Francis L., San Diego. Died December 25, 1973 in San Diego, aged 58. Graduate of the University of Chicago School of Medicine, 1942. Licensed in California in 1948. Doctor Rook was a member of the San Diego County Medical Society.

Scherb, Robert Emmett, Bakersfield. Died January 11, 1974 in Los Angeles of lung failure, aged 67. Graduate of the University of Southern California School of

Medicine, Los Angeles, 1934. Licensed in California in 1934. Doctor Scherb was a retired member of the Kern County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

SCHWARTZ, GEORGE, Beverly Hills. Died November 29, 1973, aged 69. Graduate of New York University College of Medicine, New York, 1929. Licensed in California in 1959. Doctor Schwartz was a member of the Los Angeles County Medical Association.

SIRBU, ABRAHAM B., San Francisco. Died January 12, 1974 in Stanford of heart disease, aged 70. Graduate of the University of California Medical School, Berkeley-San Francisco, 1928. Licensed in California in 1928. Doctor Sirbu was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

SORENSEN, ROY W., Victorville. Died January 24, 1974 at Mammoth Lakes of heart disease, aged 55. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1944. Licensed in California in 1947. Doctor Sorensen was a member of the San Bernardino County Medical Society.

STRICKLER, JOHN P., San Francisco. Died January 8, 1974, aged 82. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1916. Licensed in California in 1916. Doctor Strickler was a member of the San Francisco Medical Society.

VELDEE, MILTON VICTOR, Menlo Park. Died January 15, 1974 in Palo Alto, aged 83. Graduate of Harvard Medical School, Boston, 1919. Licensed in California in 1950. Doctor Veldee was a retired member of the Santa Clara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

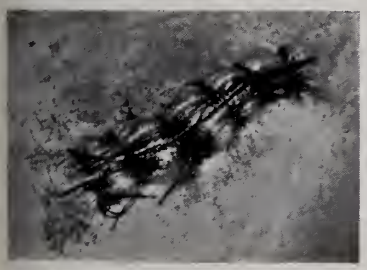
WOOD, ELDEN GLENN, Paradise. Died December 29, 1973 in Paradise of heart disease, aged 62. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1938. Licensed in California in 1938. Doctor Wood was a member of the Butte-Glenn Medical Society.

Healing nicely, but it still HURTS

HERE Burns

When parenteral analgesia is no longer required, Empirin Compound with Codeine usually provides the relief needed.

HERE Sutures



Empirin Compound with Codeine is effective for visceral as well as soft tissue pain—provides an antitussive bonus in addition to its prompt, predictable analgesia.

EMPIRIN® COMPOUND c̄ CODEINE

#3, codeine phosphate* (32.4 mg.) gr. ½
#4, codeine phosphate* (64.8 mg.) gr. 1

prescribing convenience: up to 5 refills in 6 months, at your discretion (unless restricted by state law); by telephone order in many states.

Empirin Compound with Codeine **No. 3,** codeine phosphate* 32.4 mg. (gr. ½); **No. 4,** codeine phosphate* 64.8 mg. (gr. 1). *Warning—may be habit-forming. Each tablet also contains: aspirin gr. 3½, phenacetin gr. 2½, caffeine gr. ½.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

Classified Advertisements

The rate for each insertion is **$2.50 per line** (average six words per line) **with five line minimum.**

Box number charge: $1.50 each month.

Classified display rates $25.00 per inch.

Copy for classified advertisements should be received not later than **the fifth of the month preceding issue.** • Classified advertisers using Box Numbers forbid the disclosure of their identity. Your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the rules of the Advertising Committee.

CLASSIFIED ADVERTISEMENTS ARE PAYABLE IN ADVANCE

PHYSICIANS WANTED

LOS ANGELES-ORANGE COUNTIES — Growing HMO needs more General Practitioners, Pediatricians, Orthopods, OB/GYN's and ENT. Competitive salaries, regular increases and tax-sheltered fringe benefits. Two newly opened medical centers. Send your curriculum vitae to: Frank Eaton, MD, Medical Director, Family Health Program, Room 2419, 2925 Palo Verde, Long Beach, CA 90815.

INTERNIST, GENERALIST AND UROLOGIST, State Veterans Home and Hospital. Salary depending upon training, experience and position to be filled. Excellent retirement plan and other benefits. Located one hour from San Francisco in beautiful Napa Valley. Call or write John P. Preston, Administrator, Phone (707) 944-2422.

UROLOGIST: University trained, board qualified, 14 years clinical-surgical experience with current associate professor status, seeks to relocate in a busier clinic or Urological association on or before April 15, 1974. Married. Licensed in California. All opportunities will be considered. Box 9376, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PATHOLOGIST, Associate (Los Angeles/San Fernando Valley), for acute 200-bed hospital and two rapidly expanding clinical laboratories. AP & CP board eligible or board certified. Starting salary $40-50,000 + benefits commensurate with training and experience leading to partnership. Contact: Allen N. Levy, MD; Central Diagnostic Laboratory; 7660 Gloria Avenue; Van Nuys, CA 91406; (213) 782-2300.

PHYSICIAN—Chief of Medical Services wanted for a regional diagnostic and counseling center for the developmentally disabled. Will serve as chief of clinical services and diagnostic team. California license required. Must be board certified or qualified. Salary: $26,148 - $31,788. Filing deadline: May 1, 1974. Send résumé, letter of application and references to: Neal Wade, 801 County Center No. 3 Court, Modesto, CA 95350.

FAMILY PRACTICE DOCTOR to join two doctor family practice group — four-day week, four weeks vacation plus two weeks for postgraduate studies. Suburban area near Rose Bowl-California. Prefer board or board eligible family practitioner. $3,250 per month to start and partnership after one year. Near three major hospitals. Both doctors teaching S.C. and Loma Linda Medical Schools; (213) 790-1103.

ON LOK SENIOR HEALTH SERVICES is looking for a California licensed physician interested in working with the elderly in the Chinatown-North Beach Community. (Bi-lingual preferred.) 20 hours per week. Salary up to $12,766. Send résumé: 1490 Mason Street, San Francisco, CA 94133; Tel.: (415) 989-2578.

OTOLARYNGOLOGIST PARTNERSHIP

OTOLARYNGOLOGIST, desires partnership in a group practice in San Francisco Bay area—Northern California. Boston trained; military requirement satisfied; available July 1974. Contact R. Hillel, 320 Harvard Street, Cambridge, Mass. 02139.

PRACTICES FOR SALE

LUCRATIVE OB-GYN PRACTICE located 70 miles from metro-Los Angeles must be sold immediately due to sudden death of physician. Six-year-old, well-established practice grossing $15,000 per month. Modern, fully-equipped, 800 sq. ft. office, located one-half block from large, modern medical center with open staff privileges. Will consider all offers. Contact: Lee E. Bockhacker, MD, Antelope Valley Hospital Medical Center, 1600 West Avenue J, Lancaster, CA 93534; (805) 948-4577.

MEDICAL EQUIPMENT FOR SALE

X-RAY: Picker Zephyr Superficial Therapy Unit. 140 KVP, 10 MA. Many accessories—MA Regulator. Good working condition. Immediate delivery. A. Justin Williams, MD & Associates. Phone: (415) 781-6863.

ECHOENCEPHALOSCOPE, Hewlett Packard A scan with oscilloscope camera, transducer and testmobile for measuring brain midline position. Excellent condition. Cost $3,370, make offer. Newport Beach, phone (714) 642-1437.

HOUSE TO RENT

BOLINAS, CALIFORNIA—four b.r. fully eqpt. and furn. house overlooking ocean and S.F. avail. 3 wks. to 2 mos. year round. Box 9375, Western Journal of Medicine, 731 Market, S.F., CA 94103.

PHYSICIANS

Employee Health Service needs Physicians—full time, days only. Calif. license required.

Contact: **THEODORE GREENBURG, MD**
LAC/USC Medical Center, Box 273
1200 N. State St., Los Angeles, Calif. 90033
(213) 225-3115, Ext. 71777

SOUTHERN CALIFORNIA GP, FP, INTERNIST WANTED

New 36-bed accredited hospital needs FP, GP or Internist. Work with established physician or in hospital. Central location to beaches, mountains, desert recreational areas. 25 miles to Loma Linda Medical Center. 1 hr. to Los Angeles.

Contact Administrator

Perris Valley Community Hospital
2224 Ruby Dr.
Perris, California 92370
PHONE (714) 657-5105 COLLECT

Finer
ALLERGENIC EXTRACTS

- *specialized allergy service*
- *diagnostic and therapeutic extracts*

• PROMPT •
PERSONAL SERVICE

Frees you from details and delays.
Provides you with ready-to-use extracts.
Descriptive literature sent on request.

BERKELEY BIOLOGICALS

Second & Hearst Sts., Berkeley, CA 94710
2275 W. Lincoln Ave., Anaheim, CA 92801

(Continued on Page 28)

TEXTBOOKS FOR SALE

MANUAL OF ROUTINE ORDERS FOR MEDICAL AND SURGICAL EMERGENCIES
published by
WARREN GREEN, Inc.
10 South Brentwood Boulevard
St. Louis, Missouri 63105

PHYSICIAN

Hospital residents in Pediatrics, Internal Medicine, Psychiatry, Family Medicine or in other specialties (if you have prior general medical experience) for early evening work in youth clinics. These clinics provide general medical and counseling services primarily for adolescents and young adults in eight locations within Los Angeles County. The emphasis is on caring, non-judgmental attitudes and high quality (non-academic) treatment. Sessions usually 3 to 4 hours. The pay varies with years of experience from $12.31 to $14.90 per hour. The clinical experience is unique, patients are deeply grateful for services offered and Important community health needs are being met in this program. If interested, please contact:

William L. Minkowski, MD
(213) 225-3115, Ext. 79911

PHYSICIAN

Non-resident positions with a background in general medicine for evening work in a program of eight youth clinics within Los Angeles County. General medical and counseling help is provided primarily to adolescents and young adults in a caring, non-judgmental setting. Sessions run between three and four hours. The pay scale is $50 for the first hour and one-half, $25 per hour thereafter, with a maximum of $125 for 4½ hours. If interested, please contact:

William L. Minkowski, MD
(213) 225-3115, Ext. 79911

INDUSTRIAL PHYSICIAN

Duties include providing pre-employment, executive, and special physicals and handling first aid and medical emergencies.

We would be very much interested in a physician-surgeon who would like to retire from general practice yet continue to practice medicine in a pleasant well-equipped medical facility.

The starting salary will be about $25,000. We have a 40-hour week and an exceptional benefit plan which includes income insurance and a savings plan.

Requirements: MD degree, California license, U.S. citizenship, and several years of expirience.

Please call

MR. CAREY BAKER
(213) 391-0711, Ext. 2494

HUGHES AIRCRAFT CO.
Aerospace Divisions
Culver City, California

CALIFORNIA MEDICAL ASSOCIATION

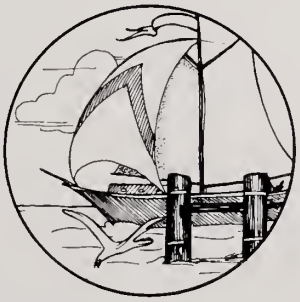
1974 Annual Postgraduate Institutes

WEST COAST COUNTIES

DEL MONTE HYATT HOUSE—MONTEREY

April 4-5, 1974

- Chemotherapy of Metastatic Neoplasia
- Clinical Application of Radioisotope Techniques
- Breast Cancer
- Dilemmas in Treating Prostatic Cancer
- Psychotropic Drugs
- Alcoholism
- General Problems in Surgery and Anesthesia
- Headaches
- Venereal Disease
- Pediatric Cardiology
- Croup



CONFERENCE ON PHYSICAL FITNESS AND SPORTS MEDICINE

HILTON INN—SAN DIEGO

April 19-20, 1974

- Physiological Effects of Exercise
- Exercise in the Diagnosis of Heart Disease
- Radiographic Diagnosis of Athletic Injuries
- Nutrition and Athletic Performance
- Heart Disease Risk Factor Modification through Multi-Media Education
- ENT Disorders in Athletics
- Conditioning of the Middle-Aged Athlete
- Problems of the Jogger
- Injections in Athletic Medicine
- Psychological Effects of Physical Conditioning
- Rehabilitation of the Coronary Heart Disease Patient
- Neurological Injury

SAN JOAQUIN VALLEY COUNTIES

THE AHWAHNEE—YOSEMITE

May 3-4, 1974

- Hypertension
- Malignant Hypertension
- The Kidney and Hypertension
- Myocardial Infarction
- Vitamin E and Coronary Heart Disease
- Coronary Bypass Grafts
- Experimental Use of Polyunsaturated Ruminant Fats
- Artificial Joint Replacement
- Sex Counselling

1974 CMA POSTGRADUATE INSTITUTES

plan to attend the following Postgraduate Institute(s):

☐ WEST COAST COUNTIES
April 4-5, Monterey

☐ SPORTS MEDICINE
April 19-20, San Diego

☐ SAN JOAQUIN VALLEY
May 3-4, Yosemite

FEE: $30 for EACH institute

Please make check payable to California Medical Association

NAME _____

ADDRESS _____

CITY _____ ZIP _____

MAIL TO: CMA, Continuing Medical Education, 731 Market Street, San Francisco, California 94103

A program and hotel reservation form will be sent to you

Synthroid®
(sodium levothyroxine)

the smooth road to thyroid replacement therapy.

Synthroid is T4. It provides your patients with what is needed for complete thyroid replacement therapy.

Free Tab-Minder sample packages available from Flint Professional Services Department.

Indications: SYNTHROID (sodium levothyroxine) is specific replacement therapy for diminished or absent thyroid function resulting from primary or secondary atrophy of the gland, congenital defect, surgery, excessive radiation, or antithyroid drugs. Indications for SYNTHROID (sodium levothyroxine) **Tablets** include myxedema, hypothyroidism without myxedema, hypothyroidism in pregnancy, pediatric and geriatric hypothyroidism, hypopituitary hypothyroidism, simple (nontoxic) goiter, and reproductive disorders associated with hypothyroidism. SYNTHROID (sodium levothyroxine) **for Injection** is indicated for intravenous use in myxedematous coma and other thyroid dysfunctions where rapid replacement of the hormone is required. The injection is also indicated for intramuscular use in cases where the oral route is suspect or contraindicated due to existing conditions or to absorption defects, and when a rapid onset of effect is not desired.

Precautions: As with other thyroid preparations, an overdosage of SYNTHROID (sodium levothyroxine) may cause diarrhea or cramps, nervousness, tremors, tachycardia, vomiting and continued weight loss. These effects may begin after four or five days or may not become apparent for one to three weeks. Patients receiving the drug should be observed closely for signs of thyrotoxicosis. If indications of overdosage appear, discontinue medication for 2-6 days, then resume at a lower dosage level. In patients with diabetes mellitus, careful observations should be made for changes in insulin or other antidiabetic drug dosage requirements. If hypothyroidism is accompanied by adrenal insufficiency, such as Addison's Disease (chronic adrenocortical insufficiency), Simmonds's Disease (panhypopituitarism) or Cushing's syndrome (hyperadrenalism), these dysfunctions must be corrected prior to and during SYNTHROID (sodium levothyroxine) administration. The drug should be administered with caution to pa with cardiovascular disease; developme chest pains or other aggravations of card cular disease requires a reduction in dosa

Contraindications: Thyrotoxicosis, acute m dial infarction. **Side effects:** The effects of THROID (sodium levothyroxine) therapy are in being manifested. Side effects, when th occur, are secondary to increased rates of metabolism; sweating, heart palpitations or without pain, leg cramps, and weight Diarrhea, vomiting, and nervousness have been observed. Myxedematous patients heart disease have died from abrupt incr in dosage of thyroid drugs. Careful obser of the patient during the beginning of an roid therapy will alert the physician to ar toward effects.

It has been shown that *Synthroid* (T_4) converts to T_3 at the cellular level to supply metabolic needs.[1, 2]

1 *Synthroid* is T_4.

2 Because T_4 converts to T_3 at the cellular level, it provides full thyroid replacement at maintenance doses.[1, 2]

3 T_4 hormone content is controlled by chemical assay.

4 *Synthroid* is assayed chemically; no biologic test is necessary to measure potency.

5 *Synthroid* provides predictable results when used with current thyroid function tests.

6 *Synthroid* is the most prescribed brand name of thyroid in the U. S. and Canada.

7 Sodium levothyroxine in *Synthroid* tablets is chemically pure. It does not contain any animal gland parts.

8 When stored properly, *Synthroid* has a longer shelf life than desiccated thyroids.

9 On a daily basis, *Synthroid* is cost competitive with other thyroid products.

The smooth road to thyroid replacement therapy.

Synthroid®
(sodium levothyroxine)

most cases with side effects, a reduction of followed by a more gradual adjustment d will result in a more accurate indication patient's dosage requirements without the ance of side effects.

e and Administration: The activity of mg. SYNTHROID (sodium levothyroxine) T is equivalent to approximately one grain , U.S.P. Administer SYNTHROID tablets ngle daily dose. In hypothyroidism with- xedema, the usual initial adult dose is . daily, and may be increased by 0.1 mg. 0 days until proper metabolic balance is d. Clinical evaluation should be made y and PBI measurements about every 90 Final maintenance dosage will usually rom 0.2-0.4 mg. daily. In adult myxedema, dose should be 0.025 mg. daily. The dose may be increased to 0.05 mg. after two weeks and to 0.1 mg. at the end of a second two weeks. The daily dose may be further increased at two-month intervals by 0.1 mg. until the optimum maintenance dose is reached (0.1-1.0 mg. daily).

Supplied: Tablets: 0.025 mg., 0.05 mg., 0.1 mg., 0.15 mg., 0.2 mg., 0.3 mg., 0.5 mg., scored and color-coded, in bottles of 100, 500, and 1000. Injection: 500 mcg. lyophilized active ingredient and 10 mg. of Mannitol, U.S.P., in 10 ml. single-dose vial, with 5 ml. vial of Sodium Chloride Injection, U.S.P., as a diluent. SYNTHROID (sodium levothyroxine) **for Injection** may be administered intravenously utilizing 200-400 mcg. of a solution containing 100 mcg. per ml. If significant improvement is not shown the following day, a repeat injection of 100-200 mcg. may be given.

1. Braverman, L. E., Ingbar, S. H., and Sterling, K.: Conversion of Thyroxine (T_4) to Triiodothyronine (T_3) in Athyreotic Human Subjects, J. Clin. Invest. *49*:855-64, 1970.
2. Surks, M. I., Schadlow, A. R., and Oppenheimer, J. H.: A New Radioimmunoassay for Plasma L-Triiodothyronine: Measurements in Thyroid Disease and in Patients Maintained on Hormonal Replacement. J. Clin. Invest. *51*:3104-13, 1972.

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015

(Continued from Page 24)

OFFICES FOR LEASE OR RENT

HEMET—For Rent—Medical suite $425, 4 examination rooms, private office, lab reception, 2 lavs. New medical center adjacent to business community and Hospital—Fast growing retirement area—Smog free—Ideal location for family man; phone (714) 658-3261.

DOCTOR'S OFFICE, 100 percent location, approximately 1,200 square feet of space. Ample parking in beautiful, growing Sonoma Valley. Previously occupied by same doctor for 18 years; call (707) 938-4332.

OFFICE FOR RENT: 2,109 sq. ft. Ideal location, center of town, across the street from large hospital. Ophthalmology suite or will partition to suit any medical practice. Write or phone Dr. Mario R. Galliano, 204 West College Street, Covina, California 91723, (213) 332-7112.

OFFICES FOR LEASE OR RENT

EUREKA—MEDICAL SUITE AVAILABLE. 1,000 to 1,300 square feet depending on need. New Professional Building adjacent to hospital. Lease available with purchase option. Excellent outdoor recreation area. Hunting, fishing, boating, hiking—you name it. Come and relax on the North Coast, (707) 443-3005.

SOUTHERN CALIFORNIA, EL TORO, Medical-Dental Building, now leasing with occupancy August 1974. Ideal location for family oriented practice. Centrally located for rapidly growing area. For information call (714) 831-1321.

ESCONDIDO, CALIFORNIA—New medical suite, 1,872 sq. ft.—suitable for Internist, Generalist or Orthopod.—one or two physicians—near hospital. Fast growing area; call (714) 747-8430.

OFFICES FOR LEASE OR RENT

SOUTHERN CALIFORNIA, LAGUNA NIGUEL—A rapidly growing area. 30,000 sq. ft. Medical Center Complex minutes from beach and equal distance from three (3) hospitals with OB-GYNS, Surgeons, Ophthalmologist, Pediatrician, General Practitioner: Need Internists, G.P. sub-specialties of Int. Medicine, ENT, Orthopedic Surgeon and Urologist. Please call for information (714) 495-4601.

PRACTICE MEDICINE IN BEAUTIFUL LOS ALTOS, CALIF., 35 miles south of San Francisco. Ideal location near hospital facilities. Brand new professional office, to be completed to your specifications. 900 sq. ft. Convenient and abundant parking. Contact by mail, Owner, 27765 Via Ventana, Los Altos Hills, CA 94022 or phone (415) 941-1044.

YOUR FUNDS COULD BE EARNING 10% INTEREST

Secured by high quality trust deeds on prime California real estate with large equities, individually recorded in your name.

You can invest from $2,500 to $100,000 and earn a minimum of 10% interest per annum (up to 12% with prepayment bonus) from the date of deposit in escrow.

Title to your investment is fully protected by a policy of title insurance from T.I.&T. Your investment is also protected by fire insurance and Realty Tax Service. Our Collection Department sends you your checks and a computerized monthly statement of your account.

So, if you want security, simplicity, and a minimum annual yield of 10%, contact our Investment Department in person, by phone, or by mail.

RELIABLE
MORTGAGE CORPORATION

320 N. Vermont Ave., L.A.
(213) 666-2525

Trusted and Respected Brokers for 24 Years

Offer open to California residents only

COMPTON FOUNDATION HOSPITAL

820 West Compton Boulevard
COMPTON, CALIFORNIA 90220
(213) 537-3070
(213) 631-1148

G. CRESWELL BURNS, M.D.
Administrator and Medical Director

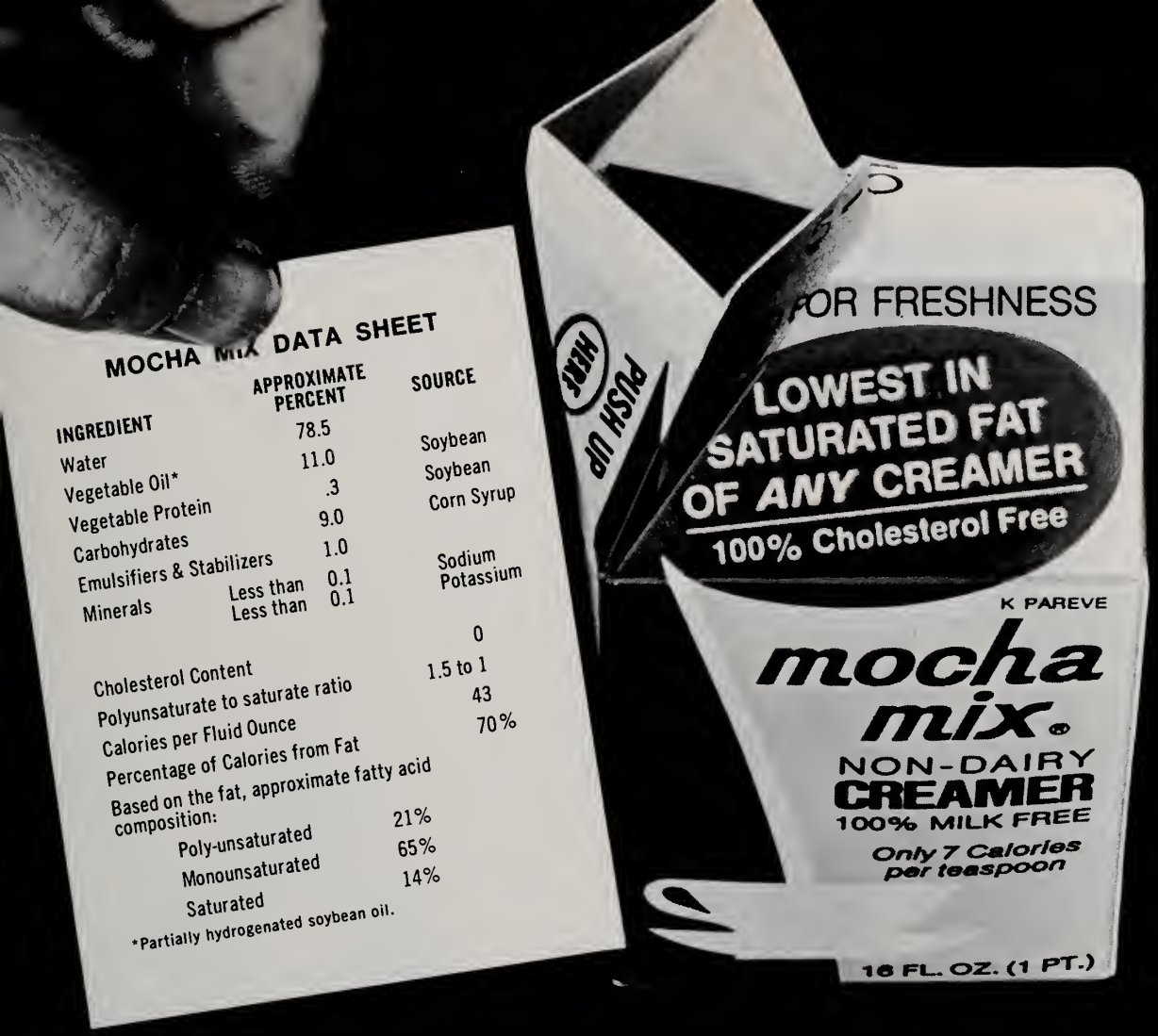
HELEN RISLOW BURNS, M.D.
Assistant Medical Director

MEMBER OF
American Hospital Association
and
National Association of Private Psychiatric Hospitals

High Standards of Psychiatric Treatment . . . Serving the Los Angeles Area

☆

Accredited by Joint Commission on Accreditation of Hospitals



Mocha Mix® presents its credentials:

Study them. Note how low Mocha Mix® is in saturated fat. (Actually the lowest of any creamer — liquid, frozen or powdered.) Then note the unsaturated to saturated fat ratio (1.5:1). And Mocha Mix is 100% milk-free and 100% cholesterol-free, too! Taste? In coffee . . . on cereal, fruit or desserts . . . or for cooking, any way, any time a creamer is called for, Mocha Mix is the most delicious creamer ever!

In addition to the 16 oz. size found in the dairy case of most grocery stores, Mocha Mix is available in larger sizes and ½ oz. portion packs for hospitals and institutions.

Interested? Send us a note and we will send you a supply of coupons your patients can redeem at their grocers. Hospital service may also be supplied upon request. Mail to: Mocha Mix Dept. Presto Food Products, Inc. P.O. Box No. 21908, Los Angeles, Calif. 90021

mocha mix the non-dairy creamer that's lowest in saturated fat!

to help treat what you often find:
obvious moderate to severe anxiety
with a less obvious underlying depression

TRIAVIL®

containing perphenazine and amitriptyline HCl

a tranquilizer–antidepressant

"...and she'd jump every time the phone rang."

"All right, I agree, she was obviously very anxious...you said she hadn't been sleeping..."

"She felt *tired enough* to sleep... not relaxed enough...food, too... she's too nervous to eat...says she *can't* relax...afraid there's something very wrong with her."

"...that's a good place to sta Did you find anything wrong with her?"

Treatment with TRIAVIL—a balanced view.

Tablets TRIAVIL are available in four different combinations affording flexibility and individualized dosage adjustment. Close supervision of patients is essential until satisfactory remission has taken place. Since suicide is a possibility in any depressive illness, patients should not have easy access to large quantities of the drug. The drug may impair alertness and potentiate the response to alcohol. It should not be used during the acute recovery phase following myocardial infarction or given to patients who have received an MAOI within two weeks. TRIAVIL should be used with caution in glaucoma and in patients prone to urinary retention. It is contraindicated in CNS depression and in the presence of evidence of bone marrow depression.

MSD MERCK SHARP & DOHME

For a brief summary of prescribing information, please turn to the following page.

a thing... negative... nothing
nically wrong. Still has a
list of somatic complaints.
ried to reassure her... to let
alk... to help her sort things
She's been in to see me a
ber of times."

"...what about medication?"

"Just what I was coming to...
I've had her on tranquilizers.
And *that's* what puzzles me. I'm
not getting the response I hoped
for. She's no better... perhaps a
little worse. It's sad to see."

"...I think *'sad'* may be what
you're not seeing! You know,
this sounds like another case
where the *anxiety* is so clear and
pervasive we tend to overlook
the depressive part of the picture.
I'm not sure that we shouldn't
almost always think of anxiety
with depression... not anxiety
alone. Take another look at your
records... talk to her some more.
If you decide she's depressed,
I think you might want to
consider TRIAVIL.... It can help
relieve her entire symptom
complex... control the anxiety...
while at the same time treat
the depression."

TRIAVIL®

containing perphenazine and amitriptyline HCl

a tranquilizer–antidepressant

to help treat what you often find:
obvious moderate to severe anxiety
with a less obvious underlying depression

Available:
TRIAVIL® 2-25: Each tablet contains
2 mg. perphenazine and 25 mg. amitriptyline HCl

TRIAVIL® 2-10: Each tablet contains
2 mg. perphenazine and 10 mg. amitriptyline HCl

TRIAVIL® 4-25: Each tablet contains
4 mg. perphenazine and 25 mg. amitriptyline HCl

TRIAVIL® 4-10: Each tablet contains
4 mg. perphenazine and 10 mg. amitriptyline HCl

INITIAL THERAPY FOR MANY PATIENTS
TRIAVIL® 2-25 (or TRIAVIL® 4-25) t.i.d. or q.i.d.

FOR FLEXIBILITY IN ADJUSTING MAINTENANCE THERAPY
TRIAVIL® 2-10 (or TRIAVIL® 4-10)

CONTRAINDICATIONS: Central nervous system depression from drugs (barbiturates, alcohol, narcotics, analgesics, antihistamines); bone marrow depression; known hypersensitivity to phenothiazines or amitriptyline. Do not give concomitantly with MAOI drugs because hyperpyretic crises, severe convulsions, and deaths have occurred from such combinations. Allow minimum of 14 days between therapies, then initiate therapy with TRIAVIL cautiously, with gradual increase in dosage until optimum response is achieved. Not recommended for use during acute recovery phase following myocardial infarction.

WARNINGS: TRIAVIL should not be given with guanethidine or similarly acting compounds. Use cautiously in patients with history of urinary retention, angle-closure glaucoma, increased intraocular pressure, or convulsive disorders. Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressants, including amitriptyline HCl, particularly in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of conduction time. Myocardial infarction and stroke have been reported with tricyclic antidepressant drugs. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. Caution patients performing hazardous tasks, such as operating machinery or driving motor vehicles, that drug may impair mental and/or physical abilities. Not recommended in children or during pregnancy.

PRECAUTIONS: Suicide is a possibility in depressed patients and may remain until significant remission occurs. Such patients should not have access to large quantities of this drug.

Perphenazine: Should not be used indiscriminately. Use with caution in patients who have previously exhibited severe adverse reactions to other phenothiazines. Likelihood of untoward actions is greater with high doses. Closely supervise with any dosage. The antiemetic effect of perphenazine may obscure signs of toxicity due to overdosage of other drugs or make more difficult the diagnosis of disorders such as brain tumor or intestinal obstruction. A significant, not otherwise explained, rise in body temperature may suggest individual intolerance to perphenazine, in which case discontinue.

If hypotension develops, epinephrine should not be employed, as its action is blocked and partially reversed by perphenazine. Phenothiazines may potentiate the action of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) and atropine. In concurrent therapy with any of these, TRIAVIL should be given in reduced dosage. May also potentiate the action of heat and phosphorous insecticides.

Amitriptyline: In manic-depressive psychosis, depressed patients may experience a shift toward the manic phase if they are treated with an antidepressant. Patients with paranoid symptomatology may have an exaggeration of such symptoms. The tranquilizing effect of TRIAVIL seems to reduce the likelihood of this effect. When amitriptyline HCl is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with 1 g of ethchlorvynol and 75-150 mg of amitriptyline HCl.

Amitriptyline HCl may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

Concurrent administration of amitriptyline HCl and electroshock therapy may increase the hazards associated with such therapy. Such treatment should be limited to patients for whom it is essential. Discontinue several days before elective surgery if possible. Elevation and lowering of blood sugar levels have both been reported.

ADVERSE REACTIONS: Similar to those reported with either constituent alone.

Perphenazine: Side effects may be any of those reported with phenothiazine drugs: extrapyramidal symptoms (opisthotonus, oculogyric crisis, hyperreflexia, dystonia, akathisia, acute dyskinesia, ataxia, parkinsonism) can usually be controlled by the concomitant use of effective antiparkinsonian drugs and/or by reduction in dosage, but sometimes persist after discontinuation of the phenothiazine.

Tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy with phenothiazines and related agents has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Involuntary movements of the extremities sometimes occur. There is no known treatment for tardive dyskinesia; antiparkinsonism agents usually do not alleviate the symptoms. It is advised that all antipsychotic agents be discontinued if the above symptoms appear. If treatment is reinstituted, or dosage of the particular drug increased, or another drug substituted, the syndrome may be masked. It has been suggested that fine vermicular movements of the tongue may be an early sign of the syndrome, and that the full-blown syndrome may not develop if medication is stopped when lingual vermiculation appears.

Other side effects are skin disorders (photosensitivity, itching, erythema, urticaria, eczema, up to exfoliative dermatitis); other allergic reactions (asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions); peripheral edema; reversed epinephrine effect, hyperglycemia; endocrine disturbances (lactation, galactorrhea, gynecomastia, disturbances of menstrual cycle); altered cerebrospinal fluid proteins; paradoxical excitement; hypertension, hypotension, tachycardia, and ECG abnormalities (quinidine-like effect); reactivation of psychotic processes; catatonic-like states; autonomic reactions, such as dry mouth or salivation, headache, anorexia, nausea, vomiting, constipation, obstipation, urinary frequency or incontinence, blurred vision, nasal congestion, and a change in pulse rate; hypnotic effects; pigmentary retinopathy; corneal and lenticular pigmentation; occasional lassitude, muscle weakness, mild insomnia. Other adverse reactions reported with various phenothiazine compounds include blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia); liver damage (jaundice, biliary stasis); grand mal convulsions, cerebral edema; polyphagia; photophobia; skin pigmentation; and failure of ejaculation.

Amitriptyline: Note: Listing includes a few reactions not reported for this drug, but which have occurred with other pharmacologically similar tricyclic antidepressant drugs. *Cardiovascular:* Hypotension; hypertension; tachycardia; palpitation; myocardial infarction, arrhythmias; heart block; stroke. *CNS and Neuromuscular:* Confusional states; disturbed concentration; disorientation; delusions, hallucinations; excitement; anxiety; restlessness; insomnia; nightmares; numbness, tingling, and paresthesias of the extremities; peripheral neuropathy; incoordination; ataxia; tremors; seizures; alteration in EEG patterns; extrapyramidal symptoms; tinnitus. *Anticholinergic:* Dry mouth; blurred vision; disturbance of accommodation; constipation; paralytic ileus; urinary retention; dilatation of urinary tract. *Allergic:* Skin rash; urticaria; photosensitization; edema of face and tongue. *Hematologic:* Bone marrow depression including agranulocytosis; leukopenia; eosinophilia; purpura; thrombocytopenia. *Gastrointestinal:* Nausea; epigastric distress; vomiting; anorexia; stomatitis; peculiar taste; diarrhea; parotid swelling, black tongue. *Endocrine:* Testicular swelling and gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido; elevated or lowered blood sugar levels. *Other.* Dizziness, weakness; fatigue; headache; weight gain or loss; increased perspiration; urinary frequency; mydriasis; drowsiness; jaundice; alopecia. *Withdrawal Symptoms:* Abrupt cessation after prolonged administration may produce nausea, headache, and malaise. These are not indicative of addiction.

OVERDOSAGE: Treatment is symptomatic and supportive. However the intravenous administration of 1-3 mg of physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. On this basis, in severe overdosage with perphenazine-amitriptyline combinations, symptomatic treatment of central anticholinergic effects with physostigmine salicylate should be considered.

For more detailed information, consult your MSD Representative or see full Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486.

MSD
MERCK SHARP & DOHME

situation:

Elderly... doesn't get out much anymore... whole world slowed down.

constipation:

Poor eating habits... often, on various constipating drugs... inactive, frequently debilitated... weakened muscles ... sluggish, atonic bowel. Result—in many oldsters—constipation.

laxation:

Gentle, predictable and easy-to-take SENOKOT Tablets or Granules. Taken at bedtime, they usually induce comfortable evacuation in the morning. Leave your older patient feeling more like getting up and around.

Supplied: SENOKOT Tablets (small, easy-to-swallow)—Bottles of 50 and 100. SENOKOT Granules (delicious, cocoa-flavored)—4, 8 and 16 ounce (1 lb.) canisters.

Senokot

(standardized senna concentrate)

Tablets/Granules

a natural laxative

Purdue Frederick

A7031 128673

© COPYRIGHT 1973 THE PURDUE FREDERICK COMPANY/NORWALK CONN. 06856

In Gonorrhea

Injection WYCILLIN®

(sterile procaine penicillin G suspension) Wyeth

Penicillin in large doses remains the drug of choice in therapy of gonorrhea. Among penicillins, first choice recommended by the national Center for Disease Control for parenteral therapy of uncomplicated gonorrhea is aqueous procaine penicillin G.

Administration of 4.8 million units together with 1 gram oral probenecid, preferably given at least 30 minutes prior to injection, is recommended in treatment of uncomplicated gonorrhea.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reaction.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings.")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated) — Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, preferably given at least 30 minutes prior to injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units. I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N gonorrhoeae.* Follow-up treatment consists of 4.8 million units daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each TUBEX® disposable syringe 2,400,000 units (4-cc. size) contains procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.7% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. The multiple-dose 10-cc. vial contains per cc. 300,000 units procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, 2 mg. polyvinylpyrrolidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Denise has VD.

Let's keep it from getting around.

Actual new cases of infectious syphilis apparently reached the 100,000 mark during the past year; new cases of gonorrhea, more than 2.5 million. That VD is rampant again is due, in large part, to the multiple contacts of teenagers like Denise.

By administering adequate doses of the recommended types of penicillin, you can usually cure VD in the beginning stages. And destroy another link in the chain of infection.

In Syphilis

Injection

BICILLIN® Long-Acting (sterile benzathine penicillin G suspension) Wyeth

Benzathine penicillin G...a drug of choice recommended by the national Center for Disease Control in all stages of syphilis and in preventive treatment after exposure.

Administration of 2.4 million units (1.2 million in each buttock) of benzathine penicillin G usually • cures most cases of primary, secondary and latent syphilis with negative spinal fluid • helps break chain of infection • minimizes chance of immediate reinfection.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular benzathine penicillin G.—Venereal infections: syphilis, yaws, bejel and pinta.

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

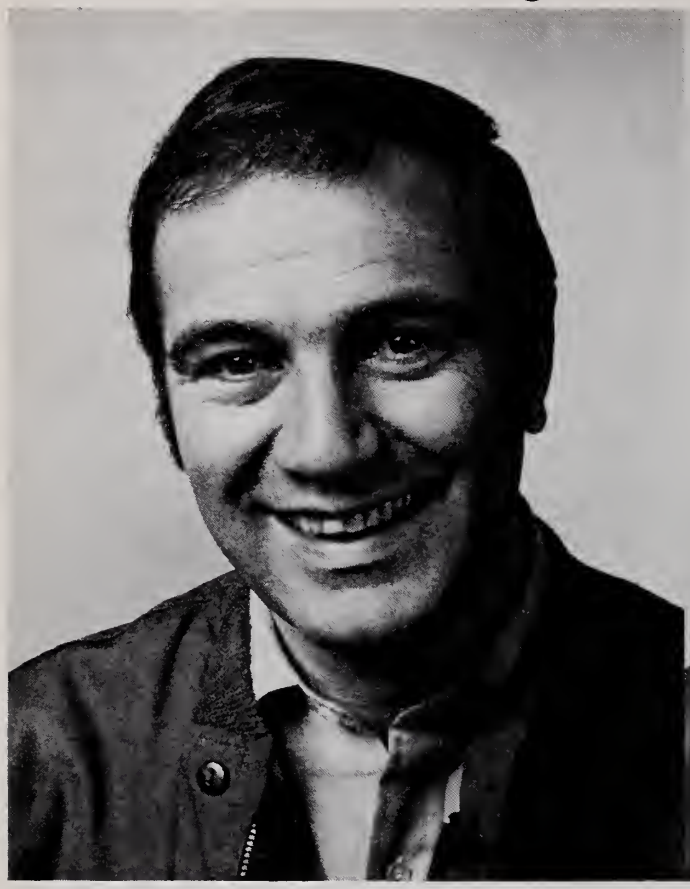
Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vignrously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: 2,400,000 units in 4-cc. single dose disposable syringe. Each TUBEX disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. Units benzathine penicillin G (as active ingredient); 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. polyvinylpyrrolidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Wyeth Laboratories · Philadelphia, Pa. 19101

Case history #3



Robert's well-being comes first.

Robert's being well comes first.

Robert is a paraplegic. On July 2, 1962, while working as a truck driver, he sustained a serious injury to his spinal cord. The resulting paraplegia made his chances for returning to work seem poor.

State Fund acted immediately, cooperating and assisting with initial treatment and commencing disability payments. The State Fund staff, including its rehabilitation specialists, assisted others in the medical community in helping this severely injured patient and his family to adjust to his disability.

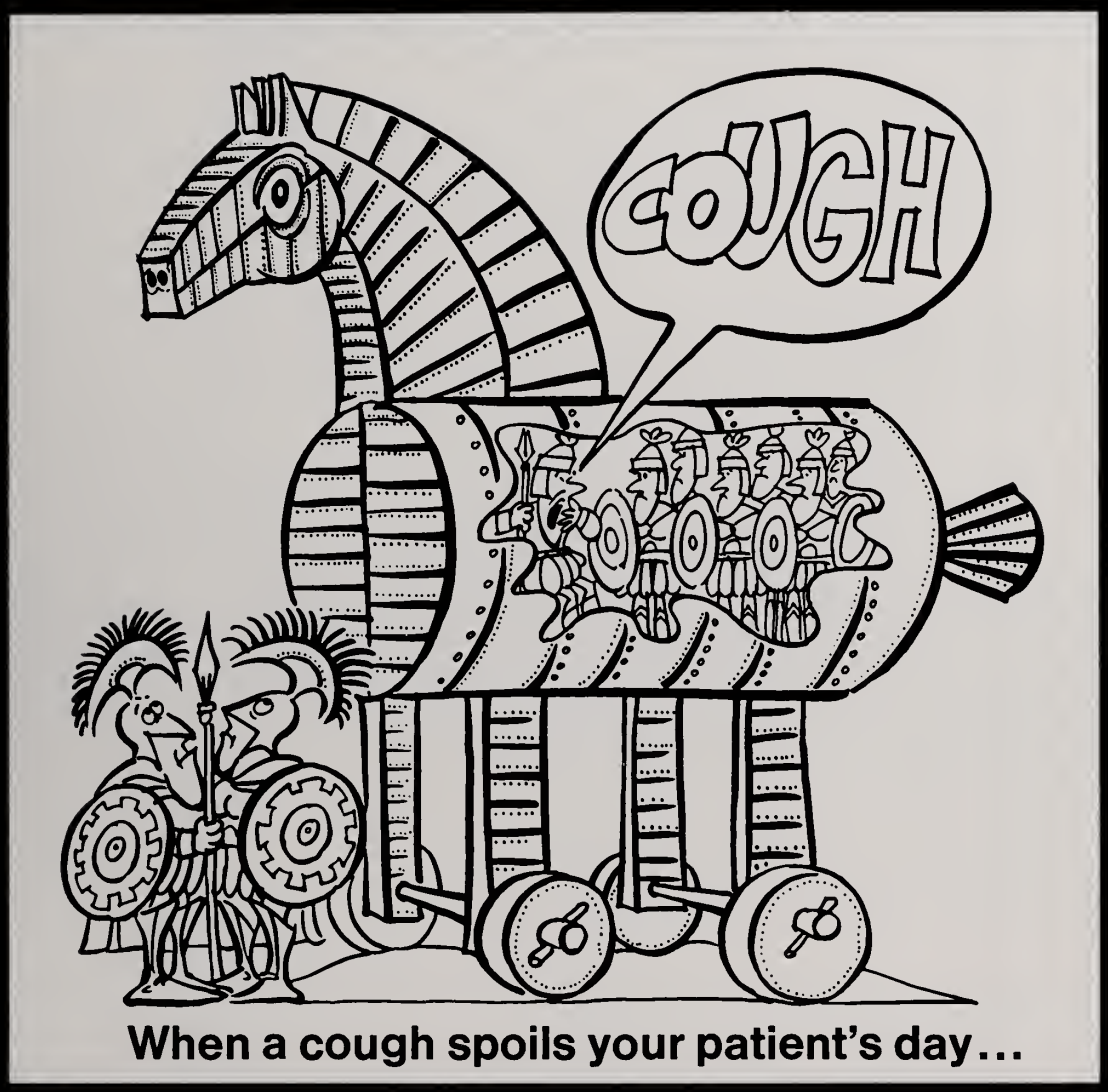
He progressed steadily in his rehabilitation. In 1970, he decided to take advantage of State Fund's *Therapeutic Capitalization* program (THERACAP). The projected cost of his total future medical needs was determined, and in cooperation with Robert, State Fund arranged for the investment of this amount in secure mutual funds.

THERACAP has given Robert and his family financial security with a potential for growth. As of March, 1973, his capital investment had increased $14,000.

Through his own courage and determination, Robert has taken advantage of the assistance available and has re-established himself as an independent and productive person. Another example of teamwork between the injured, the medical community and State Fund.

Conserving your human resources is our only business

STATE COMPENSATION INSURANCE FUND



When a cough spoils your patient's day...

Triaminic® Expectorant

Each teaspoonful (5 ml.) contains:

Triaminic, 25 mg. (phenylpropanolamine hydrochloride, 12.5 mg.; pheniramine maleate, 6.25 mg.; pyrilamine maleate, 6.25 mg.); glyceryl guaiacolate, 100 mg.; alcohol, 5%.

When an antitussive is also desired, the same formulation plus 10 mg. codeine phosphate is available as **Triaminic Expectorant with Codeine.** (A Schedule V Controlled Substance.)

The Adult Expectorant that is great for kids, too.

Dorsey Laboratories/Division of Sandoz-Wander, Inc./Lincoln, Nebraska 68501

BO–SB

Bone Marrow Transplantation Protocol

The Department of Medicine, Division of Hematology and Oncology and the Department of Microbiology and Immunology, University of California, Los Angeles, have established a Bone Marrow Transplantation Protocol for the treatment of appropriate patients with aplastic anemia, leukemia, and related disorders. Physicians wishing to refer patients should contact Robert Peter Gale, MD, or Martin Cline, MD, UCLA Medical Center, Los Angeles, California 90024 (213-825-6228, 213-825-6301 or 213-825-7865).

(Continued from Page 7)

ENDOCRINE ASPECTS OF MALNUTRITION—Marasmus, Kwashiorkor and Psychosocial Deprivation—KROC Foundation Symposia Number 1. Compiled and Edited by Lytt I. Gardner, MD, State University of New York; Upstate Medical Center, Syracuse; and Peter Amacher, PhD, The Kroc Foundation, Santa Ynez, CA. The KROC Foundation, P.O. Box 547, Santa Ynez, CA (93460), 1973. 520 pages, (no price given).

HANDBOOK OF SURGERY—Fifth Edition—Edited by John L. Wilson, MD, Professor of Surgery, Stanford University School of Medicine, Palo Alto. Lange Medical Publications, Drawer L, Los Altos (94022), 1973. 877 pages, $7.00.

IMMUNOLOGY—An Introduction to Molecular and Cellular Principles of the Immune Responses—Herman N. Eisen, MD, Professor of Immunology, Massachusetts Institute of Technology, Cambridge, Massachusetts; formerly Professor and Head, Department of Microbiology, Washington University School of Medicine, St. Louis, Missouri. Medical Department, Harper & Row, Publishers, Inc., 2350 Virginia Avenue, Hagerstown, Maryland (21740), 1974. 310 pages, Illustrated, $10.00 (Paperback).

MYOCARDIAL DISEASES—Edited by Noble O. Fowler, MD, Professor of Medicine and Director, Division of Cardiology, University of Cincinnati Medical Center. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 379 pages, $18.50.

NEONATOLOGY—Diseases of the Fetus and Infant—Edited by Richard E. Behrman, MD, Professor and Chairman, Department of Pediatrics, Columbia University College of Physicians and Surgeons; Director, Babies Hospital, The Children's Medical and Surgical Center of New York. The C. V. Mosby Company, 3301 Washington Boulevard, St. Louis, Missouri (63103), 1973. 698 pages, 215 illustrations, including one color plate, $39.50.

PODIATRIC MEDICINE—Irving Yale, DPM, Ed D (Hon.), Past President, American Podiatry Association, Past President and Fellow, American College of Foot Roentgenologists, Member, Editorial Advisory Board, **Journal of the American Podiatry Association,** formerly, Chief of Podiatry Service, Orthopaedic Section, Department of Surgery, Yale-New Haven Medical Center, Fellow, American Public Health Association, Associate Fellow, American College of Foot Surgeons. The Williams & Wilkins Company, 428 E. Preston Street, Baltimore (21202), 1974. 288 pages, $18.50.

POST-MORTEM—David M. Spain, MD, and Janet Kole. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1974. 296 pages, $7.95.

PULMONARY CARE—A Hahnemann Symposium—Edited by Robert F. Johnston, MD, Department of Medicine, Hahnemann Medical College & Hospital, Philadelphia. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 370 pages, $22.50.

RITUALS OF SURGERY—Richard Selzer, MD, Harper's Magazine Press, 2 Park Avenue, New York City (10016), 1974. 193 pages, $6.95.

A SHORTCUT TO VENERAL DISEASE EDUCATION—Joseph Chiappa, Executive Director, Greater Philadelphia Alliance for the Eradication of Venereal Disease; and Acting Executive Director, United States Alliance for the Eradication of Venereal Disease; and Gelolo McHugh, PhD., Consultant, Family Life Publications, Inc., formerly with Department of Psychology, Duke University. Family Life Publications, Inc., 219 Henderson Street, P.O. Box 427, Saluda, NC (28773), 1973. 18 pages, with 4 test sheets, 75¢ plus 15¢ postage, quantity prices on request.

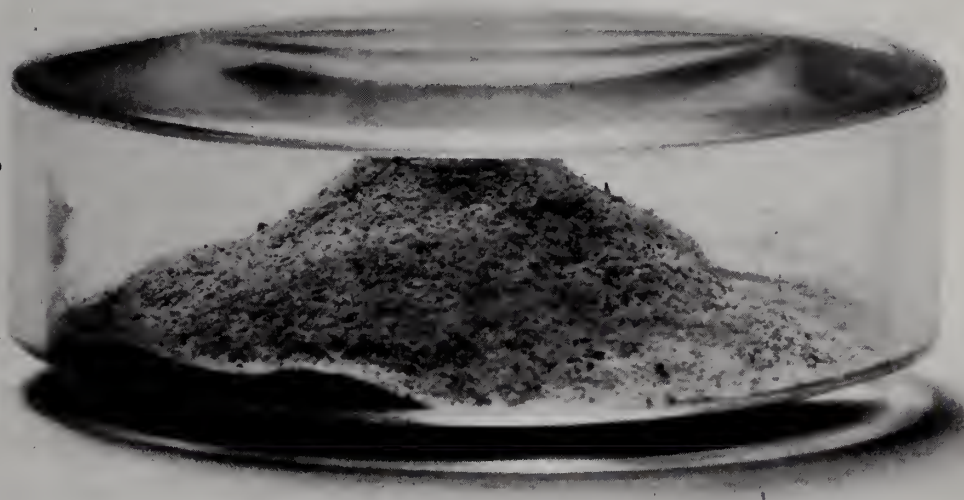
THE UNCERTAIN MIRACLE—Vance H. Trimble, Editor: **Kentucky Post and Times Star.** Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1974. 236 pages, $6.95.

WHAT TO DO ABOUT YOUR BRAIN-INJURED CHILD, or Your Brain-damaged, Mentally Retarded, Mentally Deficient, Cerebral-palsied, Emotionally Disturbed, Spastic, Flaccid, Rigid, Epileptic, Autistic, Athetoid, Hyperactive Child—Glenn Doman, Illustrations by David Melton. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1974. 291 pages, $7.95.

PROLOID® (thyroglobulin)
Caution: Federal law prohibits dispensing wi prescription.
Description. Proloid (thyroglobulin) is obta from a purified extract of frozen hog thy It contains the known calorigenically a components, Sodium Levothyroxine (T_4) Sodium Liothyronine (T_3). Proloid (thyrogl lin) conforms to the primary USP specificat for desiccated thyroid—for iodine basec chemical assay—and is also biologically sayed and standardized in animals.
Chromatographic analysis to standardiz Sodium Levothyroxine and Sodium Liot nine content of Proloid (thyroglobulin) is tinely employed.
The ratio of T_4 and T_3 in Proloid (thyro ulin is approximately 2.5 to 1.
Proloid (thyroglobulin) is stable when st at usual room temperature.
Indications. Proloid (thyroglobulin) is th replacement therapy for conditions of in quate endogenous thyroid production: cretinism and myxedema. Replacement the will be effective only in manifestations of h thyroidism.
In simple (nontoxic) goiter, Proloid (th globulin) may be tried therapeutically, in emergency situations, in an attempt to re the size of such goiters.
Contraindication. Thyroid preparations contraindicated in the presence of uncorre adrenal insufficiency.
Warnings. Thyroglobulin should not be in the presence of cardiovascular disease less thyroid-replacement therapy is clearl dicated. If the latter exists, low doses sh be instituted beginning at 0.5 to 1.0 grain to 64 mg) and increased by the same am in increments at two-week intervals. This mands careful clinical judgment.
Morphologic hypogonadism and nephr should be ruled out before the drug is ad istered. If hypopituitarism is present, the a nal deficiency must be corrected prio starting the drug.
Myxedematous patients are very sensiti thyroid and dosage should be started at a low level and increased gradually.
Precaution. As with all thyroid preparat this drug will alter results of thyroid func tests.
Adverse Reactions. Overdosage or too r increase in dosage may result in signs symptoms of hyperthyroidism, such as n strual irregularities, nervousness, cardiac rhythmias, and angina pectoris.
Dosage and Administration. Optimal dos is usually determined by the patient's clir response. Confirmatory tests include BMR ^{131}I resin sponge uptake, T_3 ^{131}I red cell take, Thyro Binding Index (TBI), and Ach Tendon Reflex Test. Clinical experience shown that a normal PBI (3.5-8 mcg/100 will be obtained in patients made clinic euthyroid when the content of T_4 and T adequate. Dosage should be started in s amounts and increased gradually with in ments at intervals of one to two weeks. U maintenance dose is 0.5 to 3.0 grains (3. 190 mg) daily.
Overdosage Symptoms. Headache, instab nervousness, sweating, tachycardia, with usual bowel motility. Angina pectoris or c gestive heart failure may be inducec aggravated. Shock may develop. Massive o dosage may result in symptoms resemb thyroid storm. Chronic excessive dosage produce the signs and symptoms of hyper roidism.
(Treatment: In shock, supportive measu should be utilized. Treatment of unrecogn adrenal insufficiency should be considered
How Supplied. ¼ grain; ½ grain; score grain; 1½ grain; scored 2 grain; 3 grain; scored 5 grain tablets, in bottles of 100 1000.
Full information available on request.
WARNER/CHILCOTT
Division, Warner-Lambert Company
Morris Plains, New Jersey 07950
PR-GP-31-B/W

IN NATURAL THYROID THERAPY:

ARE PATIENTS GETTING THE POTENCY YOU PRESCRIBE?



Unlike U.S.P. desiccated thyroid, Proloid®(thyroglobulin) offers the assurance of constant potency.

To begin with, Proloid is uniquely purified. The thyroglobulin extracted from hog thyroid is devoid of any glandular debris.

Then, Proloid is chemically and biologically assayed to assure consistent metabolic activity from batch to batch. The T_4 and T_3 content of every dose is blended for optimal thyroid replacement.

Important, too, is the fact that Proloid is invariably "fresh" when your patients take it. Under proper storage conditions, its potency will not diminish for at least four years.

All of which adds up to this: the potency of Proloid is constant...for more consistent results.

PROLOID®
(thyroglobulin)

natural thyroid therapy that leaves nothing to chance

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine,** Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

ALCOHOLISM AND DRUG USE

April 20-21—**Alcoholism and Drug Abuse: 1974.** UCSF, CMA, Haight-Ashbury Free Medical Clinic, Institute for Social Concerns at UCSF. Saturday-Sunday. $60. Contact: UCSF.

CANCER

March 16—**The People Side of Cancer—2nd Annual Rehabilitation Conference.** American Cancer Society, Calif. Division, at Airport Marina Hotel, Los Angeles. Saturday. Contact: Marie Aylward, ACS, Calif. Div., 875 O'Farrell St., San Francisco 94109. (415) 885-5822.

March 21-22—**Clinical Cancer Conference—9th Annual.** UCSF at St. Francis Hotel, San Francisco. Thursday-Friday.

April 21—**Slide Seminar on Tumors of Female Genital Tract.** See Obstetrics and Gynecology, April 21.

May 30-31—**Cancer Symposium.** USC. Thursday-Friday.

Continuously—**Tumor Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. Tuesdays, 4:00 p.m. Contact: Sidney Saltzstein, MD, University Hospital, San Diego. (714) 291-3330, ext. 1071.

Continuously — **Tumor Board — Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Pathology Conference Room, Harbor General Hospital, Torrance. Fridays 3-4 p.m. Advice and consultation from specialists in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: John Benfield, MD, Dept. of Surgery, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 281.

MEDICINE

March 15-16—**Endoscopic Instrumentation and Upper Gastrointestinal Endoscopy.** American Society for Gastrointestinal Endoscopy at Airport Sheraton Hotel, San Diego. Friday-Saturday. 16 hrs. $50 for ASGE members; $75 for nonmembers. Contact: Lee S. Monroe, MD, 476 Prospect St., La Jolla 92037. (714) 459-2390.

March 16—**Clinical Immunology in Medical Practice.** St. Mary Medical Center, Long Beach 90801. (213) 435-4441, ext. 390.

March 19-22—**Consultants' Course in Dermatology.** UCSF. 27 hrs. $150. Tuesday-Friday.

March 20—**Sickle Cell Seminar on Specialty Aspects.** Charles R. Drew Postgraduate Medical School and King-Drew Sickle Cell Center at Claude Hudson Auditorium, Los Angeles. Wednesday. Contact: Duane Dillman, EdD, Coordinator of Cont. Ed., 1620 E. 119th St., Los Angeles 90059.

March 20-May 22—**Hematology.** UCLA. 2 months; Wednesdays.

March 25-April 5—**Intensive Review of Internal Medicine.** USC. 2 weeks.

March 29-30—**Cardio-Pulmonary Seminar '74.** Heart Association of the Redwood Empire at Gibson Hall, Solano County Fairgrounds, Vallejo. Friday-Saturday. $35. Contact: Jim Wyatt, Heart Assn. of the Redwood Empire, P.O. Box 844, Santa Rosa 95402. (707) 542-1992.

April 1-10—**Cardiology for the Consultant.** American College of Cardiology at Rancho Santa Fe Inn, Rancho Santa Fe. 10 days. Contact: Miss Mary Anne McInerny, Dir., Dept. of Cont. Ed. Programs, Am. College of Cardiology, 9650 Rockville Pike, Bethesda, Md. 20014.

April 3—**Pediatric Nephrology.** See Pediatrics, April 3.

April 3-5—**Diabetes.** UCSF. Wednesday-Friday.

(Continued on Page 42)

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

situation:

mpaired cardiac status . . . straining at
tool may be hazardous. . .

constipation:

estricted physical activity . . . often,
ajor changes in customary daily
utine . . . constipating medications. . .

axation:

ENOKOT Tablets or Granules, taken at
edtime, generally induce effective, yet
omfortable evacuation in the morning
. help avoid straining.

upplied: SENOKOT Tablets (small,
asy-to-swallow)—Bottles of 50 and 100.
ENOKOT Granules (delicious, cocoa-
avored)—4, 8 and 16 ounce (1 lb.) canisters.

Senokot Tablets Granules
(standardized senna concentrate)

a natural
axative

PURDUE FREDERICK
4 THE PURDUE FREDERICK COMPANY
NLK, CONN 06856 136874

(Continued from Page 40)

April 4—**Cardiovascular Symposium—20th Annual.** Central Mission Trails Heart Association at Holiday Inn, Santa Cruz. Thursday. Contact: Lynn Putnam, Asst. Dir., 600 S. Main St., Salinas 93901. (408) 424-6007.

April 5—**Respiratory Emergency Care—Allied Health Professions Course.** PMC. Friday.

April 6—**Arthrography.** UCSF. Saturday.

April 18-19—**Coronary Rehabilitation.** USC. Thursday-Friday.

April 22—**Clinical Spectrum of Coronary Artery Disease: Diagnosis and Treatment.** Mt. Zion Hospital and Medical Center at Holiday Inn, Redding. Monday. Contact: Mt. Zion Hosp. & Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600.

April 22-26—**Medical Diagnosis and Therapeutics in Internal Medicine.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Friday.

April 24—**Clinical Spectrum of Coronary Artery Disease: Diagnosis and Treatment.** Mt. Zion Hospital and Medical Center at Doctors Hospital, Modesto. Wednesday. Contact: Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600.

April 24-26—**Present Practice and New Developments in Nuclear Medicine.** See Radiology and Pathology, April 24-26.

April 26—**Clinical Spectrum of Coronary Artery Disease: Diagnosis and Treatment.** Mt. Zion Hospital and Medical Center at Del Monte Lodge, Carmel. Friday. Contact: Mt. Zion Hosp. & Med. Ctr., P.O. Box 7921, San Francisco 94102. (415) 567-6600.

May 2-3—**Dermatology for Internists and GPs.** UCSF. Thursday-Friday.

May 9-10—**Advances in Cardiology.** USC at Huntington-Sheraton Hotel, Pasadena. Thursday-Friday.

May 15—**Sickle Cell Seminar on Current Research.** Charles R. Drew Postgraduate Medical School and King-Drew Sickle Cell Center at Claude Hudson Auditorium, Los Angeles. Wednesday. Contact: Duane Dillman, EdD, Coordinator of Cont. Ed., 1620 E. 119th St., Los Angeles 90059.

May 19-20—**Peptic Ulcer Disease.** American Gastroenterological Association at Hilton Hotel, San Francisco. Sunday-Monday. $100 for members; $125 non-members. Contact: AGA Postgraduate Course-Peptic Ulcer, 6900 Grove Rd., Thorofare, N.J. 08086.

May 19-25—**American Gastroenterological Association.** Hilton Hotel, San Francisco. Sunday-Saturday. Contact: Mr. Charles B. Slack, Exec. Sec., AGA, 6900 Grove Rd., Thorofare, N.J. 08086.

May 20-21—**Gastrointestinal Endoscopy—4th Postgraduate Course.** American Society for Gastrointestinal Endoscopy at Hilton Hotel, San Francisco. Monday-Tuesday. $75 for ASGE members; $100 for non-members. Contact: J. Alfred Rider, MD, Dir., ASGE Postgraduate Course, 350 Parnassus, Suite 900, San Francisco 94117.

May 20-22—**Heart and Lung Disease in Neonates and Infants.** UCLA at Ahwahnee Hotel, Yosemite National Park. Sunday-Wednesday. For Southern Calif. physicians only.

May 22—**American Society for Gastrointestinal Endoscopy.** Hilton Hotel, San Francisco. Wednesday. Contact: Bernard M. Schuman, MD, Sec., ASGE, 2799 W. Grand Blvd., Detroit 48202.

May 23-25—**Cardiologists' Appraisal of Cardiac Surgery.** PMC at St. Francis Hotel, San Francisco. Thursday-Saturday.

Continuously—**Clinical Conferences.** Community Hospital of Santa Cruz. See Of Interest to All, Continuously.

Continuously—**Medical Chest Conference.** St. Mary's Hospital, San Francisco. Tuesdays, 4:00-5:00 p.m. in Pulmonary Classroom. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Medical Morbidity-Mortality Conference.** St. Mary's Hospital, San Francisco. Thursdays, 12:15-1:00 p.m. in Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Clinical Cardiology Conferences.** San Diego County Heart Association at University Hospital, San Diego. Thursdays, 8-10 p.m. Contact: Robert O'Rourke, MD, Instructor, Univ. Hospital, San Diego. (714) 291-3330, ext. 1644. Or Mrs. Cathy Ware, Prog. Dir., San Diego Co. Heart Assn., 3640 5th St., San Diego 92103. (714) 291-7454.

Continuously — **Differential Diagnosis in Internal Medicine.** USC. Fourth Thursday of each month, 7:30-10:00 p.m. September 27, 1973-May 30, 1974.

Continuously—**Renal Dialysis Traineeships.** UCSF. By special arrangement.

Continuously—**Preceptorships in Biochemistry and Biophysics.** UCSF. By arrangement.

Continuously—**Clinics in Dermatology.** UCSF. By arrangement.

Continuously—**Cardiovascular Seminars.** Mondays at 4:30 p.m. in the second floor lecture hall, Basic Science Building, UCSD. Contact: UCSD.

Continuously—**Preceptorships in Cardiology.** American College of Cardiology and PMC. By arrangement. Contact: Arthur Selzer,, MD, PMC; or Miss Mary Anne McInerny, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

Continuously—**Biomedical Lecture Series.** UCSD. Specified Wednesday at 8:00 p.m. For schedule contact UCSD.

Continuously—**Joint Continuing Medical Education Programs for South Bay Hospitals.** UCSD, Bay General Hospital, Chula Vista Community Hospital, Coronado Hospital, Paradise Valley Hospital and CRMP. Programs to be held at various hospitals. Contact: UCSD.

Continuously—**Neurology Conference.** San Joaquin General Hospital, Stockton. Mondays, 10:00-11:30 a.m. in Conference Room 2. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Renal Conference.** San Joaquin General Hospital, Stockton. First Thursday of each month, 11:00 a.m. to 12:00 noon, Conference Room 2. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Wednesday of each month, 10:00-11:30 a.m., Conference Room 1. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Seminar in Clinical and Public Health Aspects of Chest Diseases.** Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Three-hour sessions on second Friday of each month, 9-12 a.m., B-3 classroom, Chest Wards. Presentation of patients demonstrating medical, social, and public health aspects of chest disease, followed by discussion of cases. Course open to physicians, nurses, social workers and personnel concerned with detection and management of patients with chest disease. No fee. Contact: Matthew Locks, MD, Dir., Chest Ward Service, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1245.

Continuously—**Training of Physicians in Modern Concepts of Pulmonary Care.** CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George C. Burton, MD, LLU.

Continuously—**Neurological Sciences.** St. Francis Hospital of Lynwood. Wednesdays, 7:30-8:30 a.m. Presentations of radiological evaluations and pathological specimens of current material and review of current topics in specialty. Weekly notification of cases available. Contact: Ralph Miller, Admin. Asst., St. Francis Hospital of Lynwood, 3620 Imperial Hwy., Lynwood 90262. (213) 639-5111, ext. 365.

Continuously—**Continuing Education in Internal Medicine—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12:00-1:00 p.m. Systematic review of internal medicine, lectures by faculty and visiting professors. Contact: A. James Lewis, MD, Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 647.

Continuously—**Training for Physicians in General Internal Medicine.** CRMP Area VI and LLU at LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

Continuously—**Basic Home Course in Electrocardiography.** One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. $125 (52 issues). Contact: USC.

Continuously—**Cardiology Conferences — CRMP Area III.** Monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations of local complicated cardiological problems. Contact: William J. Fowkes, Jr., MD, 703 Welch Road, Suite G1, Palo Alto 94304. (415) 321-1200, ext. 6015.

Grand Rounds—Medicine

Tuesdays

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

9:00-10:00 a.m., Morrissey Hall, St. Mary's Hospital, San Francisco.

Neurologist in Chief Rounds. 12:30 p.m., 6 East, University Hospital of San Diego County, San Diego. UCSD.

Wednesdays

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

1st Wednesday of each month, 10:00-11:15 a.m., Conference Room 1, San Joaquin General Hospital, Stockton.

10:30-12 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., University Hospital, UCSD.

12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

Thursdays

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

10:30-12:00 noon, Room 63-105, UCLA Medical Center. UCLA. Second, Third, and Fourth Thursdays.

Neurology. 11:00 a.m., 664 Science, UCSF.

Neurology. 12:30 p.m., University Hospital of San Diego County, San Diego. UCSD.

4th Thursday of each month, 12:30 p.m. in lower conference room, Huntington Intercommunity Hospital, Huntington Beach.

Fridays

8:00 a.m., Auditorium, First Floor, Kern County General Hospital, Bakersfield. UCLA.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. UCLA. Second and Fourth Fridays.

Neurology. 8:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

1st and 3rd Fridays, 8:30 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. UCLA.

Clinicopathologic Conference. 1st Friday, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

Internal Medicine. 2nd, 3rd, and 4th Fridays, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

MENTAL RETARDATION

May 23-24—**Aspects of Mental Retardation.** USC. Thursday-Friday.

OBSTETRICS AND GYNECOLOGY

March 24-25—**Gynecological Laparoscopy: Diagnostic and Operative.** UCI and American Association of Gynecological Laparoscopists at UCI. Sunday-Monday. $100.

March 28—**Fetal Monitoring.** Charles R. Drew Postgraduate Medical School and Martin Luther King, Jr., General Hospital at Claude Hudson Auditorium, Los Angeles. Thursday. Contact: Duane Dillman, EdD, Coordinator of Cont. Ed., 1620 E. 119th St., Los Angeles 90059.

April 9-12—**High Risk Pregnancy: Medical and Obstetrical Management.** USC at Gene Autry Hotel, Palm Springs. Tuesday-Friday.

April 10—**Infernal Triangle: Impotence, Infertility, Infections.** LLU. Wednesday.

April 16-17—**Obstetrical Laparoscopy.** Charles R. Drew Postgraduate Medical School and Martin Luther King, Jr., General Hospital at Claude Hudson Auditorium, Los Angeles. Tuesday-Wednesday. Contact: Duane Dillman, EdD, Coordinator of Cont. Ed., 1620 E. 119th St. Los Angeles 90059.

April 20—**Short Stature Symposium.** See Pediatrics, April 20.

April 21—**Slide Seminar on Tumors of Female Genital Tract.** California Tumor Tissue Registry at Hilton Hotel, Pasadena. Sunday. Contact: Weldon K. Bullock, MD, Calif. Tumor Tissue Registry, 1200 N. State St., Box 40, Los Angeles 90033.

May 6-8—**Symposium on Gynecologic Endocrinology and Infertility.** USC at Royal Lahaina Hotel, Maui. Monday-Wednesday.

Continuously—**Ob/Gyn Conference.** San Joaquin General Hospital, Stockton. Mondays, 12:00-1:30 p.m. in Doctors' Dining Room. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. See Radiology and Pathology, Continuously.

Grand Rounds—Obstetrics and Gynecology

Mondays

10-11:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Tuesdays

9:00 a.m., Fifth Floor Auditorium, Room 53-105, UCLA Medical Center. UCLA.

Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Center, Sacramento. UCD.

Fridays

8:00 a.m., Auditorium, Orange County Medical Center. UCI.

10:30 a.m., Auditorium, Women's Hospital, Los Angeles County-USC Medical Center, Los Angeles. USC.

Saturdays

8:00 a.m., Executive Dining Room, University Hospital of San Diego County, San Diego. UCSD.

PEDIATRICS

March 26-May 28—**Developing Preventive Programs for Children and Youth.** Department of Health, Health Training Resources, Berkeley. Tuesdays. Contact: Donald T. Brown, MD, Dir., 2151 Berkeley Way, Berkeley 94704.

March 29—**Sudden Death Syndrome.** USC at Childrens Hospital, Los Angeles. Friday.

April 3—**Pediatric Nephrology.** LLU. Wednesday.

April 4-5—**Conference on Management of the Child with Spina Bifida.** STAN and Crippled Children's Service Section, State Dept. of Health at STAN. Thursday-Friday.

April 15-19—**Review of Pediatrics—4th Annual.** USC at Childrens Hospital, Los Angeles. Monday-Friday.

April 20—**Short Stature Symposium.** Division of Medical Genetics, Short Stature Clinic, Harbor General Hospital at Sacramento Inn, Sacramento. Saturday. Contact: Jim Kay, 5748 Straight Way, Carmichael 95608. (916) 445-2627.

May 9-11—**Advances in Pediatrics.** UCSF. Thursday-Saturday.

May 20-22—**Heart and Lung Disease in Neonates and Infants.** See Medicine, May 20-22.

Continuously—**Perinatal Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 12:30 p.m., Conference Room. Contact: Marguerite Markarian, MD, Dir. of Nurseries, Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3261.

Continuously—**Pediatric Clinical Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 8:00 a.m., Conference Room "H." Contact: Harry W. Orme, MD, Med. Dir., Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3228.

Continuously—**Preceptorships in Pediatrics.** UCSF. By arrangement.

Continuously—**Pediatric Cardiology Conference.** UCSD, Third Floor Conference Room, University Hospital. Clinical review of cases planned for the week, Tuesdays at 7:30 a.m.; Clinical review of data obtained, Fridays at 1:30 p.m. Contact: UCSD.

Continuously—**Pediatric Research Seminar.** UCSD. Mondays, 12 noon-1:00 p.m.

Continuously—**Pediatrics Clinical Conference.** San Joaquin General Hospital, Stockton. Wednesdays, 10:00-11:15 a.m., Conference Room 3. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric-Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Thursday of each month, 9:30-11:00 a.m., Conference Room 2. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric Cardiology Conference.** St. Vincent's Hospital, Los Angeles. Last Thursday of each month, 12:00 noon, Main floor conference room. Contact: Leonard M. Linde, MD, Chief, Pediatric Cardiology, St. Vincent's Hospital, 3rd and Alvarado Sts., Los Angeles.

Continuously — **Pediatric Conference.** Cedars-Sinai Medical Center, Los Angeles. Thursdays weekly, 8:30-9:30 a.m. Contact: B. M. Kagan, MD, Lebanon Hall, Cedars-Sinai Med. Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 181.

Grand Rounds—Pediatrics

Tuesdays

8:00 a.m., Children's Hospital Medical Center, Oakland.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. UCLA.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

8:30 a.m., University Hospital of San Diego County, San Diego. UCSD.

11:30 a.m., Auditorium, Pediatric Pavilion, Los Angeles County-USC Medical Center, Los Angeles. USC.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Children's Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Children's Hospital, San Francisco.

Thursdays

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA.

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Pediatric Cardiology. 1st Friday of each month. 8:00 a.m., St. Vincent's Hospital, Los Angeles.

8-9:00 a.m., Lecture Hall, Children's Hospital of Los Angeles.

8:30 a.m., Room M104, Stanford University Medical Center, STAN.

8:30-9:30 a.m., alternately at St. Mary's, Children's, Mt. Zion, and Kaiser Hospitals, San Francisco.

9:30-11:00 a.m., Conference Room 2, San Joaquin General Hospital, Stockton.

Infectious Disease. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

PSYCHIATRY

April 3-May 1—**Group Methods.** UCSF at Federal Center, Building 3, Alameda. One month.

April 8-12—**American Orthopsychiatric Association—51st Annual Meeting.** Hilton Hotel, San Francisco. Monday-Friday. Contact: American Orthopsychiatric Assn., 1775 Broadway, New York 10019. (212) 586-5690.

April 9-13—**Psychiatric Update.** UCLA at Riviera Hotel, Palm Springs. Tuesday-Saturday.

May 18—**Suicide Prevention.** UCSF. Saturday.

Continuously—**Adolescent Case Review.** St. Mary's Hospital, San Francisco. Wednesdays, 1:00-2:00 p.m., 3 West Conference Room. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Preceptorships in Psychiatry.** UCSF. By arrangement.

Grand Rounds—Psychiatry

Wednesdays

10:30 a.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

11:00 a.m., McAuley Institute, St. Mary's Hospital, San Francisco.

RADIOLOGY AND PATHOLOGY

March 23-24—**Diagnostic Nuclear Imaging: A Review.** UCSF at Fairmont Hotel, San Francisco. Saturday-Sunday.

March 25-29—**Diagnostic Radiology—17th Annual Postgraduate Course.** UCSF at Fairmont Hotel, San Francisco. Monday-Friday. 33 hrs. $200.

April 13 — **Abnormal Laboratory Data — Thyroid Function Studies.** PMC. 8 hrs. Saturday.

April 24-26—**Present Practice and New Developments in Nuclear Medicine.** American College of Physicians at Westbury Hotel, San Francisco. Wednesday-Friday. 18 hrs. $100 for ACP members; $150 for non-members. Contact: ACP, Registrar, Postgraduate Courses, 4200 Pine St., Philadelphia 19014.

April 26-27—**Laboratory Diagnosis of Immunologic Disorders.** UCSF. Friday-Saturday. 15 hrs. $100.

May 18—**Nuclear Medicine.** UCD. Saturday.

May 31-June 2—**Radiology of the Pediatric Chest.** American College of Radiology at San Diego. Friday-Sunday. 15 hrs. $200 for members; $240 for non-members. Contact: ACR, 6900 Wisconsin Ave., Chevy Chase, Md. 20015.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. Mondays, 12:00 noon, Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Pathology Conference.** St. Mary's Hospital, San Francisco. 2nd and 4th Wednesdays. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Tumor Board.** St. Mary's Hospital, San Francisco. Mondays, 8:00-9:00 a.m., Clinic Building, Room 3. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Clinical Pathology Conference.** St. Mary's Hospital, San Francisco. Third Tuesday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Radiology Film Reading Sessions.** Orange County Radiology Society and Orange County Medical Center at Orange County Medical Center, Orange. 1st Tuesday of each month, September-June, 7:30-9:00 p.m. Contact: Edward J. Miller, MD, 301 Newport Blvd., Newport Beach. (714) 645-8600.

Continuously—**Cytopathology Seminars.** UCSF. 2nd Thursday of each month, September-June. 5:00-6:00 p.m. Contact: Eileen King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously — **Cytopathology Tutorial Program.** UCSF. Courses may be arranged throughout the year on the basis of individual needs and goals; fees are prorated accordingly. Arrangements should be discussed with instructor, Eileen B. King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two-part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

Continuously—**Scintillation Camera Workshop.** UCSF. Workshops provided for physicians and nuclear medicine technologists by special arrangement, limited to 30 trainees per workshop. One- or two-day intensive training periods, basic instruction in scintillation camera theory, scintographic principles and scintiphotographic interpretations. $50. Contact: UCSF.

Continuously — **Scintiphotograph Interpretation.** UCSF and Nuclear Medicine Section, Department of Radiology, UCSF. By special arrangement, designed to furnish physicians with an opportunity to participate in the daily activities of a university laboratory. Two-week training period participation in daily interpretation conferences, correlation conferences, routine training conferences. $175. Contact: UCSF.

Grand Rounds—Radiology-Pathology

Mondays

Pathology. 1:00 p.m., Sacramento Medical Center, Sacramento. UCD.

Tuesdays

Radiology. 3rd Tuesday of each month, 8:00 a.m., Bothin Auditorium, Children's Hospital and Adult Medical Center, San Francisco.

SURGERY AND ANESTHESIOLOGY

March 16—**Postgraduate Refresher Course—Surgery and Surgical Anatomy of the Head and Neck.** International College of Surgeons, So. Calif. Division, at Los Angeles Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Darline Murphy, Ex. Sec., ICS, So. Calif. Div., 136 N. Brighton, Burbank 91506. (213) 846-0669.

March 16-17—**Los Angeles County Society of Anesthesiologists —XIX Postgraduate Assembly.** Hilton Hotel, Los Angeles. Saturday-Sunday. 15 hrs. $50 for members; $60 non-members; $50 military; $20 students, residents, interns. Contact: Virginia Connor, Exec. Secy., LACSA, 184 N. Canon Dr., Beverly Hills 90210. (213) 275-4315.

March 17-29—**Temporal Bone Surgical Dissection Course.** Los Angeles Foundation of Otology, Los Angeles. 13 days. $1,000; $750 for residents. Contact: Jack L. Pulec, MD, L.A. Foundation of Otology, 2130 W. 3rd St., L.A. 90057.

March 18-20—**G. Mosser Taylor Course in Orthopedic Surgical Anatomy—Spine.** LLU. Monday-Wednesday.

March 20-23—**Conference on Management of Trauma.** UCLA at Riviera Hotel, Palm Springs. Wednesday-Saturday.

March 23-27—**Conference on Controversial Areas in Surgery.** UCLA at Riviera Hotel, Palm Springs. Saturday-Wednesday.

March 28-30—**General Surgery.** UCSF at Hilton Hotel, San Francisco, Thursday-Saturday.

April 7-19—**Temporal Bone Surgical Dissection Course.** Los Angeles Foundation of Otology. 13 days. $1,000; $750 for residents. Contact: Jack L. Pulec, MD, L.A. Foundation of Otology, 2130 W. 3rd St., L.A. 90057.

April 10—**Management of Acute Trauma.** UCSF at Community Hospital, Santa Cruz. Wednesday.

April 17-21—**Vascular Surgery—2nd Annual.** UCLA at Riviera Hotel, Palm Springs. Wednesday-Sunday.

April 18—**Anesthesia.** California Society of Anesthesiologists, Inc., at Regency Hyatt Hotel, San Francisco. Thursday. Contact: CSA, 100 S. Ellsworth Ave., Suite 411, San Mateo 94401. (415) 343-4644.

(Continued on Page 48)

The Weight of Professional Opinion

It's time for action to defend the laws and regulations that protect your patients against drug substitution.

These professional and trade organizations are united in supporting antisubstitution statutes and regulations:

- The American Academy of Dermatology
- The Board of Directors of the American Academy of Family Physicians
- The Executive Board of the American Academy of Neurology
- The Committee on Drugs of the American Academy of Pediatrics
- The American College of Allergists
- The Executive Committee of the American College of Obstetricians and Gynecologists
- The Board of Regents of the American College of Physicians
- The Board of Trustees of the American Dental Association
- The Board of Trustees of the American Medical Association
- The American Psychiatric Association
- The Executive Committee of the National Association of Retail Druggists
- The Board of Directors of the Pharmaceutical Manufacturers Association
- The National Wholesale Druggists' Association

Joint Statement on Antisubstitution Laws and Regulations

The purpose of this statement is to affirm the support of the participating organizations for the laws, regulations and professional traditions which prohibit the unauthorized substitution of drug products.

Traditionally, physicians, dentists and pharmacists have worked cooperatively to serve the best interests of patients. Productive cooperation has been achieved through mutual respect as well as a common concern for the ideals of public service. This mutual respect has been reflected, in part, by joint support over the years for the adoption and enforcement of laws and regulations specifically prohibiting unauthorized substitution and encouraging joint discussion and selection of the source of supply of drug products. The basic principles of medical, dental and pharmacy practice are thus utilized and preserved in the interest of patient welfare.

The antisubstitution laws have not obstructed enhancement of the professional status of pharmacy any more than they have in and of themselves guaranteed absolute protection from unsafe drugs, or freed physicians, dentists and pharmacists from their responsibilities to patients. As a practical matter, however, such laws and regulations encourage interprofessional communications regarding drug product selection and assure each profession the opportunity to exercise fully its expertise in drug usage, to the advantage of patients.

Physicians and dentists should be urged to increase the frequency and regularity of their contacts with pharmacists in selection of quality drug products, recognizing that economies to patients can be improved through such communication, taking into account the patients' needs. The pharmacist's knowledge of the chemical characteristics of drugs, their mode of action, toxic properties and other characteristics that assist in making drug selection decisions should be utilized to the fullest extent practicable by physicians and dentists in serving their patients.

Since drug product selection entails knowledge derived from clinical experience, the physician's and dentist's roles in product selection remain primary and do not permit delegation of decisions requiring medical and dental judgments. A broader role in therapy will evolve for pharmacists as improved understanding and cooperation among the professions continue to grow.

There has been no evidence that there are convincing reasons to modify or repeal existing laws and regulations prohibiting the unauthorized substitution of another drug product for the one specified by a prescriber. It is our belief that such laws and regulations merit the joint support of the medical, dental and pharmaceutical professions and the pharmaceutical industry.

Add your opinion to the weight of other professionals and send it to your state assemblyman or legislator.

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W., Washington, D. C. 20005

(Continued from Page 45)

April 20—**Surgical Anatomy and Surgery of the Abdomen.** International College of Surgeons, Southern Calif. Division, at Los Angeles Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Darline Murphy, Ex. Sec., ICS, So. Calif. Div., 136 N. Brighton, Burbank 91506. (213) 846-0669.

April 26—**Anesthesia.** California Society of Anesthesiologists, Inc., at Newporter Inn, Newport Beach. Friday. Contact: CSA, 100 S. Ellsworth Ave., Suite 411, San Mateo 94401. (415) 343-4644.

April 27—**Acupuncture in Anesthesia.** California Society of Anesthesiologists, Inc., at Hilton Hotel, Los Angeles. Saturday. Contact: CSA, 100 S. Ellsworth Ave., Suite 411, San Mateo 94401. (415) 343-4644.

April 28-May 5—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

May 2-3—**Ocular Pharmacology and Therapeutics.** UCLA, Jules Stein Eye Institute, at Neuropsychiatric Institute Auditorium, UCLA. Thursday-Friday. Contact: Bradley R. Straatsma, MD, or Leonard Apt, MD, Course Chairmen, Jules Stein Eye Institute, UCLA Sch. of Med., Los Angeles 90024. (213) 825-5053.

May 3-4—**Trauma.** UCSF at Mary's Help Hospital, Daly City. Friday-Saturday.

May 4-11—**14th Biennial Western Conference on Anesthesiology.** Princess Kaiulani Hotel, Honolulu. One week. Contact: Murray G. Atnikov, MD, Sec-Treas., Biennial Western Conf. of Anesthesiology, 2574 W. 33rd Ave., Vancouver 13, B.C.

May 5-8—**Rhinoplasty.** UCLA. Sunday-Wednesday.

May 9-11—**Neurosurgery.** UCSF at Hilton Hotel, San Francisco. Thursday-Saturday. 21 hrs. $100.

May 10-12—**Low Back Pain.** UCLA. Friday-Sunday.

May 17—**Neurology.** USC. Friday.

May 18—**Surgical and Clinical Anatomy of the Vascular System.** International College of Surgeons, So. Calif. Division, at Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Darline Murphy, Ex. Sec., 136 N. Brighton, Burbank 91506. (213) 846-0669.

May 23-25—**Cardiologists' Appraisal of Cardiac Surgery.** See Medicine, May 23-25.

May 30-June 2—**California Society of Anesthesiologists Inc.—Annual Scientific Meeting.** Sahara Tahoe Hotel, Lake Tahoe. Wednesday-Saturday. 15 hrs. Contact: Norman R. Catron, Ex. Sec., 100 S. Ellsworth Ave., Suite 400, San Mateo 94401. (415) 343-4644.

Continuously—**Basic Science Lecture Series.** Dept. of Surgery, St. Mary's Hospital, San Francisco. Mondays, 11:15 a.m.-12:15 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Mini Residencies in Orthopaedics.** STAN. Postgraduate traineeships of 4-14 days duration, as you wish. No tuition but donations accepted. Contact: Orthopaedic Division, Dept. of Surgery, Stanford.

Continuously—**Orthopedic Lecture Series.** Alternately at St. Mary's, St. Joseph's, Mary's Help, VA Martinez, Kaiser San Francisco, and Harkness Memorial Hospitals. Third Tuesday of each month, 6:00 p.m. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Orthopedic Trauma Conference.** USC at Los Angeles County-USC Medical Center. Mondays, 7:00-9:00 p.m. Contact: Dept. of Orthopedics, USC School of Med., 2025 Zonal Ave., Los Angeles 90033. (213) 225-3131.

Continuously—**Preceptorships in General Surgery.** UCSF. By arrangement.

Continuously—**Preceptorships in Neurological Surgery.** UCSF. By arrangement.

Continuously—**Preceptorships in Urology.** UCSF. By arrangement.

Continuously—**Training for Physicians in Nephrology.** CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Stewart W. Shankel, MD, LLU.

Continuously—**Surgical Anatomy.** St. Mary's Hospital, San Francisco. Mondays, 4:30 p.m., St. Mary's Hall, 2 W. Classroom. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Cline Clinic.** St. Mary's Hospital, San Francisco. Mondays, 1:30 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Morbidity and Mortality Conference.** 4th Monday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Surgical Pathology Conference.** See Radiology/Pathology, Continuously.

Continuously—**Thoracic Surgery Conference.** San Joaquin General Hospital, Stockton. Fourth Wednesday of each month, 9:00-10:30 a.m., Conference Room 1. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Medical Surgical Combined Conference.** San Joaquin General Hospital, Stockton. Second Wednesday of each month, 10:00-11:15 a.m., Conference Room 1. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Orthopaedic Audio-Synopsis Foundation.** A nonprofit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Twelve monthly c-60 cassette tapes. Annual subscription rate $72 ($36 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

Grand Rounds—Surgery

Mondays

9-10 a.m., Morrissey Hall, St. Mary's Hosiptal, San Francisco.

Tuesdays

Orthopedic Surgery. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:00-10:00 a.m., San Joaquin General Hospital, Stockton.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. UCLA.

3:30 p.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

Neurology and **Neurosurgery.** 11:00-12:15, Room 663, Science Building, UCSF.

Fridays

1:00-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego, UCSD.

Urology. 8:00 a.m., 3rd floor conference room, University Hospital of San Diego County, San Diego. UCSD.

Orthopedics. 8:00-9:00 a.m. St. Mary's Hospital, San Francisco.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA.

Orthopedics. 10:00 a.m. Auditorium of the Children's Division, Los Angeles County-USC Medical Center. The third Saturday of each month. USC.

OF INTEREST TO ALL PHYSICIANS

March 16—**Postgraduate Refresher Course—Surgery and Surgical Anatomy of the Head and Neck.** See Surgery, March 16.

March 16—**Psychiatry for GPs.** UCSF at Napa State Hospital, Imola. Saturday.

March 16—**Clinical Immunology in Medical Practice.** See Medicine, March 16.

March 28-31—**California Speech and Hearing Association—22nd Annual Conference.** Sahara Tahoe Hotel, Lake Tahoe. Thursday-Sunday. Contact: Lucille Hilger, CSHA, 1845 Green St., No. 202, San Francisco. (415) 922-1000, ext. 331.

March 29—**Organizing and Conducting Committees.** PMC. Friday. For directors of medical education.

March 30—**Urologic Problems in General Practice.** UCD. Saturday.

April 1-May 27—**Problem Oriented Medical Records.** UCLA. 8 weeks, Monday evenings.

April 4-5—**West Coast Counties Regional Postgraduate Institute.** California Medical Association at Del Monte Hyatt House, Monterey. Thursday-Friday. Contact: Richard Manley, CMA.

April 10—**The Infernal Triangle: Impotence, Infertility, Infections.** See Obstetrics and Gynecology, April 10.

April 16-18—**Family Practitioners: Heart Oriented Clinical Office Practice.** UCLA. Tuesday-Thursday.

April 18-20—**Eighth National Congress on the Socio-Economics of Health Care.** American Medical Association at Town and Country Hotel, San Diego, Thursday-Saturday. Contact: AMA, 535 N. Dearborn St., Chicago 60610.

April 19-20—**Conference on Physical Fitness and Sports Medicine.** California Medical Association at Hilton Inn, San Diego. Friday-Saturday. Contact: Richard Manley, CMA.

April 20—**Short Stature Symposium.** See Pediatrics, April 20.

April 20—**The Role of Nutrition in Medicine.** UCD. Saturday.

April 22-28—**An Introduction to Diving Medicine.** UCSF at VA Hospital, Fresno. Wednesday-Sunday.

April 26—**Educational Methodology I—Simulation and Video.** PMC. Friday. For directors of medical education.

May 2-3—**Dermatology for Internists and GPs.** See Medicine, May 2-3.

May 3-4—**San Joaquin Valley Counties Regional Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite National Park. Friday-Saturday. Contact: Richard Manley, CMA.

May 8—**Clinic on Obesity.** UCSF at Community Hospital, Santa Cruz. Wednesday.

May 11—**Current Concepts in Drug Therapy for the Practicing Physician—5th Annual Symposium in Clinical Pharmacology.** STAN, Palo Alto Medical Clinic, Palo Alto Medical Research Foundation at Stanford. Saturday.

May 15—**Office Orthopedics.** Alameda-Contra Costa Chapter, Calif. Academy of Family Physicians, at Edgewater Hyatt House Hotel, Oakland. Wednesday. Contact: Gordon Benner, MD, 3000 Colby St., Berkeley. (415) 848-7533.

May 15—**Changing Patterns in the Practice of Medicine—Annual Medical Staff Symposium.** Memorial Hospital Medical Center of Long Beach. Wednesday. Contact: H. David Mosier, MD, Prog. Comm. Chrm., Memorial Hosp. Med. Ctr., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3236.

May 18—**Suicide Prevention.** See Psychiatry, May 18.

Continuously—**Clinical Problems in Daily Practice: Physiological Basis and Practical Management.** UCSF at Chinese Hospital, San Francisco. 1st Tuesday of each month; 8:00-9:30 p.m. Mar.—Some Medical & Surgical Aspects of Acute and Chronic Renal Failure; Apr.—Practical Approach to Diagnosis & Management of Stroke; May—A Critical Overview of Antibiotic Therapy; June—The Patient in Respiratory Failure; July—Diabetes Mellitus; Aug.—Congestive Heart Failure; Sept.—Jaundice; Oct. & Nov.—to be announced.

Continuously—**Clinical Conferences.** UCSF and Community Hospital of Santa Cruz at Community Hospital, Santa Cruz. 2nd Wednesday of each month, Oct. 10, 1973-June 12, 1974, 11:00 a.m.-2:30 p.m. 27 hours. $50 for series; $7.50 per lecture. Mar.—Fluid and Electrolyte Workshop; Apr.—Management of Acute Trauma; May—Clinic on Obesity; June—The Impotent Male and the Liberated Female.

Continuously—**Emergency Medicine.** USC. Wednesdays, 7:30-9:30 p.m.

Continuously—**Bedside Clinics.** See Medicine, Continuously.

Continuously—**Family Health Program—Southern California.** 2925 N. Palo Verde, Long Beach. Second Friday of each month. 1:00-2:00 p.m. Contact: UCI.

Continuously — **Lecture Program.** Riverside-San Bernardino Chapter, American Academy of Family Physicians and UCI at Ram's Horn Inn, San Bernardino. 3rd Thursday of each month. 7:30 p.m. Contact: UCI.

Continuously—**Lecture Program.** UCI and Orange County Chapter, American Academy of Family Physicians at Saddleback Inn, Santa Ana. 2nd Monday of each month, 7:30 p.m. Contact: UCI.

Continuously—**Hospital Lecture Program.** UCI at Anaheim Mem. Hosp.; Brea Comm. Hosp.; Fountain Valley Comm. Hosp.; Garden Park Gen. Hosp., Anaheim; Hartland Comm. Hosp., Baldwin Park; Huntington Intercomm. Hosp., Huntington Beach; Imperial Gen. Hosp., Inglewood; La Habra Comm. Hosp.; La Mirada Comm. Hosp.; Los Alamitos Gen. Hosp.; Mission Comm. Hosp., Mission Viejo; Palm Harbor Hosp., Garden Grove; Rio Hondo Mem. Hosp., Downey; San Gabriel Valley Comm. Hosp., San Gabriel; Stanton Comm. Hosp.; Studebaker Comm. Hosp., Norwalk; West Anaheim Gen. Hosp.; Westminster Comm. Hosp. Contact: UCI.

Continuously—**Professional Education Program.** Porterville State Hospital. Contact: Frank McCarry, MD, P.O. Box 2000, Porterville. (209) 784-2000.

Continuously—**Round Tables with Pacific Medical Center.** PMC and Sonoma Valley Hospital at Sonoma Valley Hospital, Sonoma. Second Monday of each month in Dining Room of the hospital, 8:00-10:00 p.m. $100 per series, $15 per session. Contact: William J. Newman, MD, P.O. Box B, Sonoma 95476. (707) 996-3621.

Continuously—**Basic Science Lecture Series.** UCSD Mondays, 4:00 p.m., third floor conference room, University Hospital of San Diego County, San Diego. Contact: UCSD.

Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $75 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

Continuously—**Medical Media Network.** Programs and study guides produced in association with faculties of major medical schools and centers throughout California. MMN administered by University Extension, UCLA. Subscriptions for all California hospitals, rental or purchase, 16 mm, super 8 mm, one-inch videotape. Provides physicians throughout the state with current educational programs in local hospitals. Consult the nearest MMN Hospital regarding time and date for viewing. Contact: Mr. David E. Caldwell, Exec. Dir., MMN, 10995 Le Conte Ave., Los Angeles 90024. (213) 825-1791.

Continuously—**Stanford Speaker's Bureau for Environmental Topics.** Stanford University Committee for Environmental Information. Provides on request speakers and programs on environmental topics. Air pollution, water pollution and water conservation issues, radiation hazards and radiation technology, pesticides and their ecological problems, medicine's responsibilities in the environmental-ecology crisis and others. Contact: STAN.

Continuously—**Stanford-Mills Memorial Hospital Continuing Education Program.** STAN at Mills Memorial Hospital, San Mateo. Tuesday-Friday weekly. Basic Science for the Clinician, Grand Rounds, Intensive Care. Contact: STAN.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

FAMILY PRACTICE

April 17-19—**Sommer Memorial Lectures.** Benson Hotel, Portland.

MEDICINE

April 24—**Traumatic Emergencies.** Corvallis. Contact: Circuit Course Program, Oregon Medical Association. 4 Credits OAFP and OMA. Tuition $20.

May 15-17—**Combined American College of Emergency Physicians, Emergency Department Nurses Association, and Emergency Medical Technicians.** Contact: Donald L. McNeill, MD, Good Samaritan Hospital, 1015 N.W. 22nd, Portland 97210.

OBSTETRICS AND PEDIATRICS

April 10 and 11—**Pediatric and Ob Emergencies.** Eugene and Bend. Contact: Circuit Course Program, Oregon Medical Association. 4 Credits OAFP and OMA. Tuition $20.

SURGERY

April 3 and 4—**Medical and Surgical Emergencies.** Pendleton and LaGrande. Contact: Circuit Course Program, Oregon Medical Association. 4 Credits OAFP and OMA. Tuition $20.

MEDICAL GRAND ROUNDS

April 2—7:00 p.m.—Providence Hospital, Portland—The Clinical Significance of Bile Salt Metabolism.

April 11—5:00 p.m.—Providence Hospital, Portland—Depression Symposium.

April 24—8:00 a.m.—Providence Hospital, Portland—Multi-Element Echocardiography.

May 21—7:00 p.m.—Providence Hospital, Portland—Consequences and Cures of the Use of Prescription Drugs.

OF INTEREST TO ALL PHYSICIANS

April 5-7—**Oregon Medical Association Mid-Year Meeting.** Inn at Otter Crest at Otter Rock, Oregon. Contact: J. A. Kronenberg, Associate Executive Director, Oregon Medical Association, 2164 S.W. Park Place, Portland 97205.

WASHINGTON, MONTANA and ALASKA

REGIONAL MEDICAL PROGRAM

THIS LISTING of continuing medical education activities in Washington, Montana, and Alaska is supplied by Washington/Alaska Regional Medical Program. In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

March 14-15—**Rehabilitation Medicine Course.** UW at University Towers Hotel, Seattle. Thursday-Friday. 13 hrs. $35. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

March 14-16—**Workshop in Clinical Neurology and Neurosurgery.** W/A RMP at Holiday Inn, Everett. Thursday-Friday. Contact: Neurological Associates, Pacific & Colby Building, 1515 Pacific, Everett 98201. (206) 259-0029.

March 14-16—**North Pacific Pediatric Society—Spring Meeting.** Washington Plaza Hotel, Seattle. Thursday-Saturday. Contact: C. Patrick Mahoney, MD, The Mason Clinic, 1118 9th Ave., Seattle 98101. (206) 623-3700.

March 15-17—**Radiology of the Skeletal System.** American College of Radiology at Seattle. Friday-Sunday. 15 hrs. $200 for ACR members; $240 for non-members. Contact: ACR, 6900 Wisconsin Ave., Chevy Chase, Md. 20015.

March 16-17—**Sports Medicine Clinic—7th Annual.** W/A RMP at Sea-Tac Motor Inn, Seattle. Saturday-Sunday. 11 hrs. $50. Contact: Mr. Wayne Rasmussen, 5409 17th Ave., NW, Seattle 98107. (206) 782-3383.

March 22-23—**Dermatology: A Practical Approach to Common Problems.** Virginia Mason Medical Center. Friday-Saturday. 9 hrs. $50. Contact: Kenneth R. Wilske, MD, Dir., CME, Virginia Mason Med., Ctr., 111 Terry Ave., Seattle 98101. (206) 623-3700.

March 29—**Fetal Intensive Care.** UW at Child Development and Mental Retardation Center. Friday. 6½ hrs. $25. Con-

tact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

April 11-13—**Diagnostic Radiology.** Sacred Heart Medical Center, Spokane. Thursday-Saturday. 18 hrs. $60. Contact: Clyde A. Stevenson, MD, Sacred Heart Medical Center, Spokane 99204. (509) 455-3330.

April 18-19. **Neurology and Psychiatry.** Thursday-Friday. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. School of Med. E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

April 19—**Tacoma Surgical Club—Annual Meeting.** Univ. of Puget Sound, Tacoma. Friday. Contact: Thomas J. Miskovsky, MD, 919 South 9th, Tacoma 98405. (206) MA 7-7143.

April 25-26—**Repiratory Care.** Health Sciences Thursday-Friday. 13 hrs. $75. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

April 26-27—**Clinical Cancer Conference.** Friday-Saturday. $50. Edgewater Inn. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

April 29-30. **Exercise Testing Workshop.** Monday-Tuesday. $80. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

May 2-3—**Death and Dying.** Health Sci. Audit., Thursday-Friday. 13 hr. Fee not set. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

May 6-10—**Emergency Medicine for Career Emergency Physicians.** UW. Monday-Friday. 43 hrs. $200. Contact: Richard L. Reimer, Asst. Dir., E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 11-12—**Diagnostic and Therapeutic Radiology.** Pacific Northwest Radiological Society Annual Meeting. Washington Plaza Hotel, Seattle. Saturday-Sunday. Contact: Arthur R. Griffin, MD, 455 Medical-Dental Bldg., Seattle 98101. (206) 682-2218.

May 12-16—**American Association of Plastic Surgeons.** Olympic Hotel, Seattle. Sunday-Thursday. Contact: Maurice J. Jurkiewicz, Emory University Affiliated Hospital, 69 Butler St., S.W., Atlanta, Georgia 30303.

May 15-17—**Advances in Internal Medicine.** Wednesday-Friday. Health Sciences. 18 hrs. $75. Contact: Richard L. Reimer, Asst. Dir., E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 16-17—**Kids and More in '74.** Thursday-Friday. 13 hrs. Fee not set. Contact: William O. Robertson, Children's Orthopedic Hospital, 4800 Sandpoint Way, Seattle 98105. (206) 634-5072.

May 17-18—**Problems in Gastrointestinal Surgery.** Friday-Saturday. Virginia Mason Medical Center Auditorium. 9 hrs. $35. Contact: Kenneth Wilske, MD, Dir., CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA3-3700 ext. 470.

May 24-25—**Hypertension: Etiology and Factors in Choice of Drugs.** Friday-Saturday. Virginia Mason Clinic Medical Center Auditorium. 13 hrs. $50. Contact: Kenneth Wilske, MD., Dir. CME, Virginia Mason Clinic Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA3-3700 ext. 470.

May 30-June 1—**Washington Academy of Family Physicians Annual Meeting.** Holiday Inn, Spokane. Thursday-Saturday. Contact: John P. Plastino, MD, 6th Ave. Medical Bldg., Spokane 99204.

Index to The Western Journal of Medicine Advertising

Bank of America 19

Books Received 7, 38

Breon Laboratories, Inc.
Bronkotabs ..... Back Cover

Burroughs Wellcome Co.
Empirin Compound/Codeine 23

CMA Annual Postgraduate Institutes 25

Classified 24, 28

Compton Foundation 28

Dorsey Laboratories
Triaminic Syrup 20
Triaminic Expectorant 37

Flint Laboratories
Synthroid 26, 27

Geigy Pharmaceuticals
Tofranil PM 12, 13, 14

Lakeside Laboratories, Inc.
Norpramin 17, 18

Eli Lilly and Company
Ilosone Liquid 22

Mead Johnson Laboratories
Vasodilan 16

Marion Laboratories, Inc.
Nico-400 ..... 2, 3

Merck Sharp & Dohme
Triavil 30, 31, 32

McNeil Laboratories
Parafon Forte 6, 7

Pharmaceutical Manufacturers Association
Prescription Ads 46, 47

PVO International
Saffola 15

Presto Food Products, Inc.
Mocha Mix 29

The Purdue Fredrick Company
Senokot (Drug-Induced) 5
Senekot (Geriatric) 33
Senekot (Cardiac) 41

Reliable Mortgage Corporation 28

Roche Laboratories
Valium ..... 2nd Cover and Page 1

Security Pacific National Bank 21

G. D. Searle & Co.
Lomotil ..... 52 and Inside Back Cover

Smith Kline & French Laboratories
Ornade 11

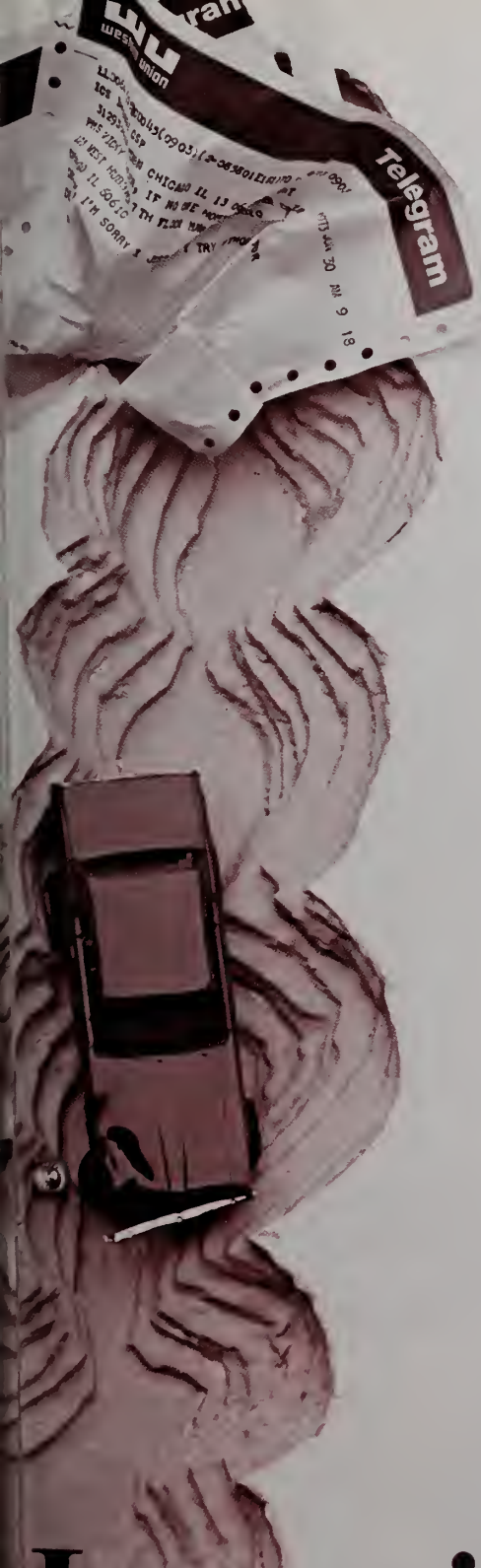
State Compensation Insurance Fund 36

Syntex Laboratories, Inc.
Aarane 8, 9, 10

Warner-Chilcott Laboratories
Proloid 38, 39

Wyeth Laboratories
Bicillin/Wycillin 34, 35

The irritations of man's day are often reflected in his gut.
The causes of irritable colon and the diarrheal symptoms that often accompany it can be as diverse as the systemic and emotional irritations man is faced with daily.
Although the mucoid nature of stools and the occurrence of diarrheal episodes coincident with times of emotional stress may be valuable clues to the functional nature of the disorder, irritable colon must often be diagnosed by exclusion. Such diagnostic exploration takes time. Discovery of the nature of any emotional problems may take more. During that time, Lomotil® is an ideal agent for controlling diarrheal symptoms.
Lomotil tablets are small, easy to carry and easy to take. They act promptly and effectively. Secondary effects are relatively infrequent and, once the first force of the diarrhea is controlled, maintenance is frequently effective on as little as one fourth of the initial dosage.
These same characteristics make Lomotil useful in controlling the diarrhea associated with gastroenteritis, antibiotic therapy and acute infections.



Lomotil®

TABLETS/LIQUID

Each tablet and each 5 ml. of liquid contain:
diphenoxylate hydrochloride . . . 2.5 mg.
(Warning: May be habit forming)
atropine sulfate . . . . . 0.025 mg.

takes care of the gut issue in irritable colon

IMPORTANT INFORMATION: *This is a Schedule V substance by Federal law; diphenoxylate HCl is chemically related to meperidine. In case of overdosage or individual hypersensitivity, reactions similar to those after meperidine or morphine overdosage may occur; treatment is similar to that for meperidine or morphine intoxication (prolonged and careful monitoring). Respiratory depression may recur in spite of an initial response to Nalline® (nalorphine HCl) or may be evidenced as late as 30 hours after ingestion. LOMOTIL IS NOT AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN. THIS MEDICATION SHOULD BE KEPT OUT OF REACH OF CHILDREN.*

Indications: Lomotil is effective as adjunctive therapy in the management of diarrhea.

Contraindications: In children less than 2 years, due to the decreased safety margin in younger age groups, and in patients who are jaundiced or hypersensitive to diphenoxylate HCl or atropine.

Warnings: Use with caution in young children, because of variable response, and with extreme caution in patients with cirrhosis and other advanced hepatic disease or abnormal liver function tests, because of possible hepatic coma. Diphenoxylate HCl may potentiate the action of barbiturates, tranquilizers and alcohol. In theory, the concurrent use with monoamine oxidase inhibitors could precipitate hypertensive crisis.

Usage in pregnancy: Weigh the potential benefits against possible risks before using during pregnancy, lactation or in women of childbearing age. Diphenoxylate HCl and atropine are secreted in the breast milk of nursing mothers.

Precautions: Addiction (dependency) to diphenoxylate HCl is theoretically possible at high dosage. Do not exceed recommended dosages. Administer with caution to patients receiving addicting drugs or known to be addiction prone or having a history of drug abuse. The subtherapeutic amount of atropine is added to discourage deliberate overdosage; strictly observe contraindications, warnings and precautions for atropine; use with caution in children since signs of atropinism may occur even with the recommended dosage.

Adverse reactions: Atropine effects include dryness of skin and mucous membranes, flushing and urinary retention. Other side effects with Lomotil include nausea, sedation, vomiting, swelling of the gums, abdominal discomfort, respiratory depression, numbness of the extremities, headache, dizziness, depression, malaise, drowsiness, coma, lethargy, anorexia, restlessness, euphoria, pruritus, angioneurotic edema, giant urticaria and paralytic ileus.

Dosage and administration: ***Lomotil is contraindicated in children less than 2 years old.*** Use only Lomotil liquid for children 2 to 12 years old. For ages 2 to 5 years, 4 ml. (2 mg.) t.i.d.; 5 to 8 years, 4 ml. (2 mg.) q.i.d.; 8 to 12 years, 4 ml. (2 mg.) 5 times daily; adults, two tablets (5 mg.) t.i.d. to two tablets (5 mg.) q.i.d. or two regular teaspoonfuls (10 ml., 5 mg.) q.i.d. Maintenance dosage may be as low as one fourth of the initial dosage. Make downward dosage adjustment as soon as initial symptoms are controlled.

Overdosage: Keep the medication out of the reach of children since accidental overdosage may cause severe, even fatal, respiratory depression. Signs of overdosage include flushing, lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, tachycardia and respiratory depression which may occur 12 to 30 hours after overdose. Evacuate stomach by lavage, establish a patent airway and, when necessary, assist respiration mechanically. Use a narcotic antagonist in severe respiratory depression. Observation should extend over at least 48 hours.

Dosage forms: Tablets, 2.5 mg. of diphenoxylate HCl with 0.025 mg. of atropine sulfate. *Liquid,* 2.5 mg. of diphenoxylate HCl and 0.025 mg. of atropine sulfate per 5 ml. A plastic dropper calibrated in increments of ½ ml. (total capacity, 2 ml.) accompanies each 2-oz. bottle of Lomotil liquid.

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Address medical inquiries to:
G. D. Searle & Co., Medical Department
Box 5110, Chicago, Illinois 60680

When the asthmatic can anticipate the attack

Bronkotabs®

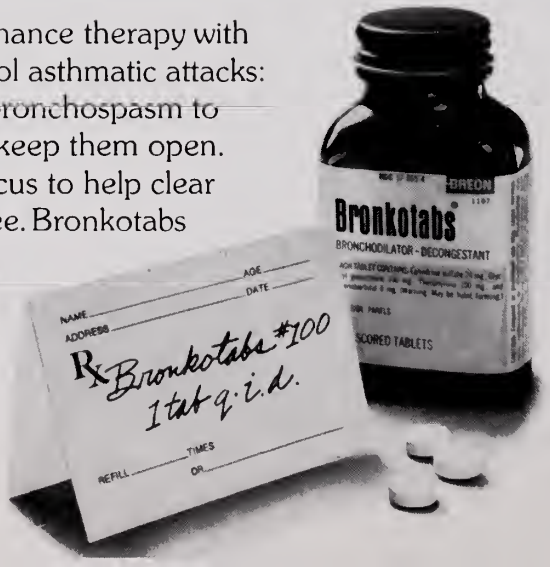
Each tablet contains ephedrine sulfate 24 mg; theophylline 100 mg; glyceryl guaiacolate 100 mg; phenobarbital 8 mg (warning: may be habit-forming).

can help forestall or relieve it

Why day to day maintenance therapy with Bronkotabs helps control asthmatic attacks:

Bronkotabs relieves bronchospasm to open airways and help keep them open.

Bronkotabs thins mucus to help clear the tracheobronchial tree. Bronkotabs decongests bronchiolar mucosa to improve the passage of air. Economical long-term therapy.



PRECAUTIONS AND ADVERSE EFFECTS: Sympathomimetic side effects are minimal, and there are none of the dangers or side effects associated with steroid therapy. However, frequent or prolonged use may cause nervousness, restlessness or sleeplessness. Should be used with caution in the presence of hypertension, heart disease or hyperthyroidism. Drowsiness may occur. Ephedrine may cause urinary retention, especially in the presence of partial obstruction, as in prostatism.

DOSAGE: Adults, one tablet every three or four hours, four or five times daily. Children over six, one-half the adult dose. Children under six, as directed.

SUPPLIED: Bottles of 100 and 1,000 tablets.

BREON

BREON LABORATORIES INC.
90 Park Avenue, New York, N.Y. 10016

LIBRARY OF MEDICINE
BOSTON
1974

THE WESTERN Journal of Medicine

VOLUME 120 • NUMBER 4 **APRIL 1974**

273 *Reproduction in Hemophilia* CAROL K. KASPER, MD, and LANCE PARTON, BS

278 *High Bulk Diet for Diverticular Disease of the Colon* ALEX. G. SHULMAN, MD

282 *Endotracheal Tube Perforation of the Hypopharynx*
DONALD B. HAWKINS, MD, DAVID C. SELTZER, MD, THOMAS E. BARNETT, MD, and GEORGE B. STONEMAN, MD

MEDICAL PROGRESS
287 *Coxa Plana (Legg-Perthes Disease)* ELMER E. SPECHT, MD

SPECIALTY CONFERENCE
295 *Ventricular Septal Defect in Infancy*
Participants: WILLIAM F. FRIEDMAN, MD, and PAUL T. PITLICK, MD
From the Weekly Pediatric Grand Rounds, University of California, San Diego, School of Medicine, University Hospital of San Diego County

MEDICAL STAFF CONFERENCE
301 *Iatrogenic Cushing's Syndrome* Discussion by JOHN D. BAXTER, MD

307 IMPORTANT ADVANCES IN CLINICAL MEDICINE—*Psychiatry*

314 EDITORIALS • *More on PSRO's* • *Legg-Calvé-Perthes* • *Biological Uniqueness and the Quality of Life* • *Treatment of Ventricular Septal Defect*

CASE REPORTS
317 *Hepatic Artery Injury in Non-Penetrating Trauma* PETER TUXEN, MD, and LUCIAN BUSCAGLIA, MD

319 *Cardiac Arrest Due to Extreme Tachycardia with Wolff-Parkinson-White Syndrome*
RICHARD L. COSKEY, MD, and RONALD DANZIG, MD

322 *Immunotherapy with Transfer Factor in Disseminated Coccidioidal Osteomyelitis and Arthritis*
PAUL CLONINGER, MD, LAURI D. THRUPP, MD, GAYLE A. GRANGER, PhD, and HAROLD S. NOVEY, MD

326 LETTERS TO THE EDITOR

SPECIAL ARTICLE
329 *The Medical Investigation of Alleged Rape*
IRVING ROOT, MD, WENDELL OGDEN, MD, and WAYNE SCOTT, MD

TRAUMA ROUNDS
334 *The Role of Hyperalimentation in Patients with Multiple Injuries*
Chief Discussant: GEORGE F. SHELDON, MD; Editors: DONALD D. TRUNKEY, MD, and F. WILLIAM BLAISDELL, MD

SPECIAL ARTICLE
338 *Caveats for PSRO's* KERR L. WHITE, MD

INFORMED OPINION
344 *PSRO and Options for the Future* PAUL J. SANAZARO, MD

INFORMATION
348 CLINICAL CARDIOLOGY: *Suppressed Plasma Renin Activity and Primary Aldosteronism*
PAUL I. JAGGER, MD

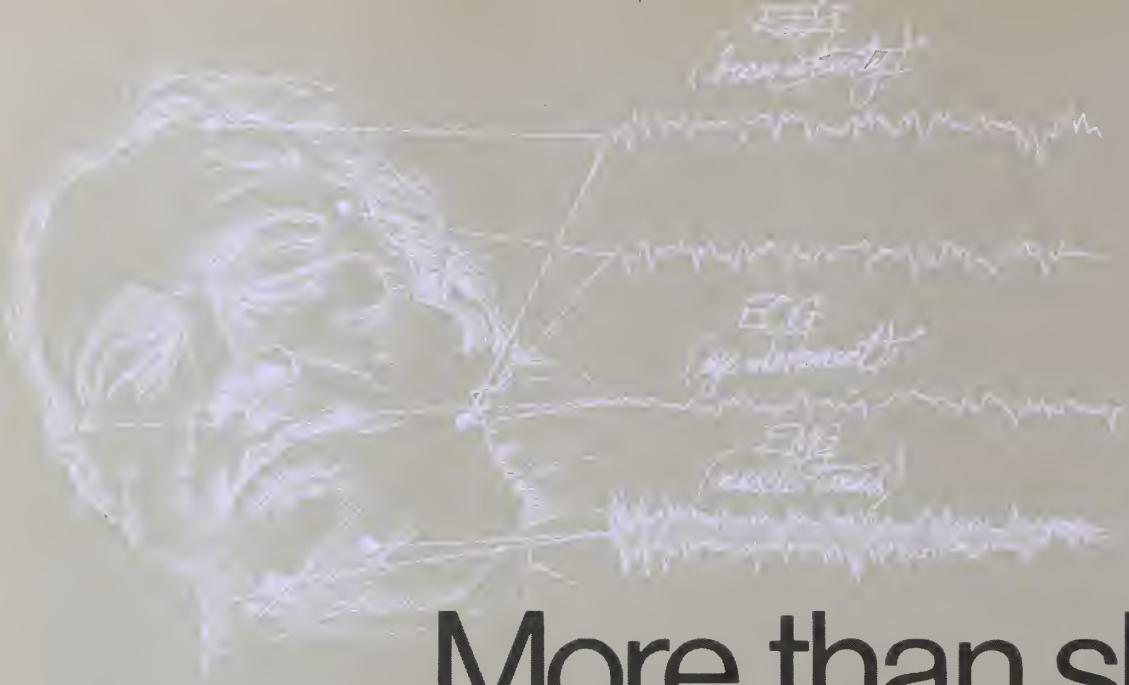
349 *Diabetic Rehabilitation Center*

350 *Book Reviews*

352 *In Memoriam*

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII; OREGON; WASHINGTON, MONTANA, AND ALASKA**
(See Advertising Page 48)

EXCHANGE OFF
FRANCIS A COUNTWAY LIB
10 SHATTUCK
BOSTON MA 02115



More than sleep.

your choice of sleep medication is wisely based on more than sleep-inducing potential

sleep with relative safety

Chronic tolerance studies have confirmed the relative safety of Dalm (flurazepam HCl); no depression of cardiac or respiratory func was noted in patients administered recommended or higher d for as long as 90 consecutive nights.

In most instances when adverse reactions were reported, they were mild, infrequent and seldon quired discontinuance of therapy. Morning "hang-over" with Dalmane has been relatively infrequent. D ness, drowsiness, lightheadedness and the like have been the side effects noted most frequently, particularly in the elderly and debilitated. (An initial dose of Dalmane 15 mg should be prescribed for these patients.)

sleep for 7 to 8 hou without need to repeat dosage

No sleep n cation has been as rigorously evaluated in the sleep research laboratory as Dalmane. Insomnia pat given one 30-mg capsule of Dalmane at bedtime, on average: fell asleep within 17 minutes, had fewer n time awakenings, spent less time awake after sleep onset, and slept for 7 to 8 hours with no need to re dosage during the night.

THE FRANKLIN COUNTY
LIBRARY OF MEDICAL
CENTER
APR 22 1974

sleep with consistency

Dalmane has been shown to be consistently effective even during consecutive nights of administration, with no need to increase dosage.

Dalmane (flurazepam HCl) is a distinctive sleep medication—a benzodiazepine specifically indicated for insomnia. It is not a barbiturate or methaqualone, nor is it related chemically to any other available hypnotic.

When your evaluation of insomnia indicates the need for a sleep medication, consider Dalmane—a single entity nonnarcotic, nonbarbiturate agent proved effective and relatively safe for relief of insomnia.

DALMANE®
(flurazepam HCl)
When restful sleep is indicated

One 30-mg capsule *h.s.*—usual adult dosage
(15 mg may suffice in some patients)
One 15-mg capsule *h.s.*—initial dosage for elderly or debilitated patients.

Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening, in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage. 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

ROCHE

ROCHE LABORATORIES
Div., Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

THE WESTERN Journal of Medicine

Since 1902 • Formerly California Medicine

OWNED AND PUBLISHED BY THE CALIFORNIA MEDICAL ASSOCIATION
731 MARKET ST. • SAN FRANCISCO, CA 94103 • TELEPHONE (415) 777-2000

editorial communications to:
MALCOLM S. M. WATTS, M.D., *Editor*

business communications to:
LYTTON O. HETLAND, *Business Manager*

. . .

LLOYD H. SMITH, JR., M.D., *Associate Editor*
ROBERT F. EDWARDS, *Managing Editor*
DAVID GREER, *Associate Managing Editor*

Editorial Board

Chairman of the Board
Malcolm S. M. Watts, San Francisco

Allergy
Norman Shure, Los Angeles
Abba I. Terr, San Francisco

Anesthesiology
Ronald L. Katz, Los Angeles

Dermatology
George F. Odland, Seattle
Rees B. Rees, San Francisco
Richard B. Stougbton, La Jolla

General and Family Practice
Robert L. Hippen, San Diego
Herbert A. Holden, San Leandro

General Surgery
Frederick M. Anderson, Reno
Richard E. Gardner, San Francisco
Lucius D. Hill, Seattle

Industrial Medicine and Toxicology
Thomas H. Milby, Berkeley

Internal Medicine
Robert J. Bolt, Davis
J. David Bristow, Portland
Marcus A. Krupp, Palo Alto
Robert G. Petersdorf, Seattle
Donald W. Petit, Los Angeles
Edgar Wayburn, San Francisco
Nathan J. Zvaifler, San Diego

Neurology
Pierre M. Dreyfus, Davis
Robert A. Fishman, San Francisco
Phillip D. Swanson, Seattle

Obstetrics and Gynecology
Ralph C. Benson, Portland
William J. Dignam, Los Angeles
Ernest W. Page, San Francisco

Ophthalmology
David O. Harrington, San Francisco
Robert S. Hepler, Los Angeles

Orthopedics
Rodney K. Beals, Portland
John A. Blosser, Oakland
Paul E. McMaster, Beverly Hills

Otolaryngology
Mansfield F. W. Smitb, San Jose
Paul H. Ward, Los Angeles

Pathology
Richard L. Kempson, Stanford
Averill A. Liebow, San Diego

Pediatrics
Robert E. Greenberg, Los Angeles
William L. Nyhan, San Diego
Henry R. Shinefield, San Francisco
Paul F. Wehrle, Los Angeles

Pharmacology
Sydney M. Finegold, Los Angeles
Kenneth L. Melmon, San Francisco

Physical Medicine and Rehabilitation
Elizabeth S. Austin, Los Angeles
Glenn G. Reynolds, San Jose

Plastic Surgery
Richard L. Dakin, San Rafael
N. John Wilde, Fresno

Psychiatry
Carl Eisdorfer, Seattle
Leon J. Epstein, San Francisco
George L. Mallory, Los Angeles
Helen Tausend, Los Angeles

Public Health
J. M. Stubblebine, Sacramento
Irma M. West, Sacramento

Radiology
H. Joachim Burhenne, San Francisco
Robert B. Engle, Pasadena
Melvin M. Figley, Seattle

Thoracic and Cardiac Surgery
John E. Connolly, Irvine
Albert Starr, Portland

Urology
Thomas F. Conroy, San Mateo
Ruben F. Gittes, La Jolla

Consultants in Medical Services and Health Care
Gerald A. Besson, Sunnyvale
Paul Scholten, San Francisco

Policy Committee—Editorial Board

STANLEY A. MOORE ..... San Diego
CARL GOETSCH ..... Berkeley
JOSEPH F. BOYLE ..... Los Angeles
HENRY V. EASTMAN ..... Tustin
E. KASH ROSE ..... Napa
ALBERT G. CLARK ..... San Francisco
MALCOLM S. M. WATTS ..... San Francisco

Advertisements—THE WESTERN JOURNAL OF MEDICINE is published the first week of each month. Advertising copy must be received not later tban the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee.

SALES REPRESENTATIVES: JOHN H. HARLING, INC.

EAST:
SAUL HORNIK
655 AMBOY AVENUE
WOODBRIDGE, N.J. 07095
TEL. (201) 636-7150

MIDWEST:
JOHN HARLING • JAMES ANTON
18 SO. MICHIGAN AVE.
CHICAGO, ILL. 60603
TEL. (312) 641-0755

WEST:
MELVIN B. TYLER
731 MARKET ST.
SAN FRANCISCO, CA. 94103
TEL. (415) 777-2000

Copyright, 1974, by the California Medical Association.

All material subject to this copyrigbt appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the non-commercial purpose of scientific or educational advancement.

Subscription prices, $8 ($9 for foreign countries); student subscription $4; single copies 80 cents.

Volumes begin with the first of January and the first of July. Subscriptions may commence at any time.

Change of Address—Requests for change of address should give both the old and new address.

CONTRIBUTIONS OF SCIENTIFIC AND ORIGINAL ARTICLES

Responsibilities for Statements and Conclusions in Original Articles—Authors are responsible for all statements, conclusions and methods of presenting their subjects. Tbese may or may not be in harmony with the views of the editorial staff. It is aimed to permit authors to have as wide latitude as the general policy of the Journal and the demands on its space may permit. The right to reduce, revise or reject any manuscript is always reserved.

Exclusive Publication—Articles are accepted for publication on condition that they are contributed solely to this Journal. Ordinarily contributors will be notified within 60 days if a manuscript is accepted for publication. Every effort will be made to return unused manuscripts.

Length of Articles—Ordinarily articles should not exceed 3,000 words (approximately 5 printed pages). Under exceptional circumstances only will articles of over 4,000 words be published.

Manuscripts—Manuscripts should be typewritten, double spaced and the original typescript plus one copy submitted.

Illustrations—Ordinarily publication of 2 or 3 illustrations accompanying an article will be paid for by THE WESTERN JOURNAL OF MEDICINE. Any number beyond this might have to be paid for by the author.

References—Should conform to the following order: name of author, title of article, name of periodical, with volume, inclusive pages, month and year—i.e.: Lee GS: The heart rhythm following therapy with digitalis—In theory and practice. Arch Int Med 44:554-562, Dec 1942. They should be listed in the order in which they are cited in the text, numbered in sequence and punctuated as above.

Reprints—Reprints must be paid for by the author at established standard rates.

CONTRIBUTIONS OF "LETTERS TO THE EDITOR"

The Editorial Board will be glad to receive and consider for publication letters containing information of general interest to physicians or presenting constructive criticisms on issues of the day.

"Entered as second class matter at the post office in San Francisco and additional mailing offices under the Act of March 3, 1879." Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized August 10, 1918.

Bank of America gives fast relief from financial upset three ways:

1. Professional Term Loans. Suffering from lack of funds to update our equipment, remodel or expand our quarters—or just want some xtra working capital on-hand? Our nancing is designed to meet your pecial needs, promptly and painssly, and with flexible terms. (For nose just starting practice, financing ased on projected income is also vailable.) And your Bank of America oan Officer can assist you with leaseold improvements, too.

2. Professional Billing and BankAmericard® Services. Give your business a shot in the arm with one of the most sophisticated financial control systems available. Our customized services streamline bookkeeping, can boost efficiency and profits, and help all aspects of your practice run more smoothly. At a cost that's easy to swallow.

3. Personal Trust Services. Expert management of stocks and bonds, real estate, property and tax matters is your prescription for financial security and peace of mind. Our Trust Officer will work out a plan tailor-made to the individual needs of your family.

With over two decades of administering to the financing needs of medical professionals, you could call us the "Money Specialists." (No other bank can offer you this much experience.) Shouldn't you make an appointment for your financial checkup with Bank of America today? You'll feel a lot better tomorrow.

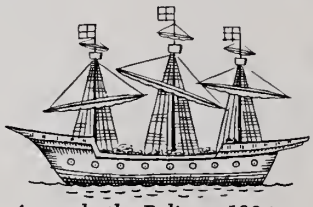
BANK OF AMERICA

OF AMERICA NT&SA · MEMBER FDIC

SIR FRANCIS DRAKE

He knew what wine can do and so should you

Sir Francis Drake, 1540?-1596



. . . formerly the Pelican, 100 tons . . .

. . . greeted by clamorous sea lions . . .

Francis Drake, wine lover and gentleman pirate, reached the shores of *Calphurnia,* as the cartographers then spelled it, in his good ship the *Golden Hind,* formerly the *Pelican,* on a foggy June 17, 1579. He was greeted by clamorous sea lions and amazed Miwok Indians.

We California winegrowers were not yet here to welcome him with a toast in California wine – but luckily, Drake brought his own. The *Golden Hind* was fairly bursting her seams with 2,130 jars of wine and 30 tons of solid silver bars, all donated, quickly and courteously, by Spanish ships overtaken enroute by this terror of the seas they knew as *Franco Draque.*

Wine Around the World – Wine, in Drake's incredible three-year exploit, was more than just treasure, drink, food, and companion to uncharted loneliness. It was almost life itself: tonic, tranquilizer, aid in care and comfort to the sick, a vehicle for remedies such as lime juice against scurvy, and happy proof against mutiny.

Coming ashore (we're not sure of the exact spot, but it was close to our Golden Gate), Drake met the *Great Hióh,* Miwok king of California. The sandy-haired, genial skipper delivered a lecture about heaven and Queen Bess. Awestruck, *Hióh* abdicated and presented Drake with California – the whole thing.

Drake accepted our state, renamed it *New Albion,* had *"a Plate of Brasse"* struck off and nailed to *"a great and firme poste,"* deeding this entire realm over to *"HERR MAIESTY QVEEN ELIZABETH OF ENGLAND AND HERR SVCCESSORS FOREVER."*

Drake spent five weeks as California's first tourist and settler. His crew unloaded the Golden Hind's rich booty, careened her, caulked her, reloaded and refloated her. Sailing July 23, 1579, they paused at *"certaine Ilands"* (Alcatraz? Angel? The Farallones?) to take aboard some *"seales"*—then on around the world!

Back in England, the saucy little pirate ship bore her skipper up the Thames to London, fame, fortune, and Knighthood. Elizabeth I, herself, came aboard and dubbed him Sir Francis with her gilded sword. (The *Golden Hind* stayed there at Thames side, a sort of national shrine; was long a floating restaurant, with gourmet foods and wines; eventually disappeared, thanks to the loving hands of souvenir seekers.)

As for Sir Francis, whose experience had proved what wine can do for sailors in travail, for all mankind . . . he could now enjoy his cup of wine with breakfast, his pint of claret or Rhenish with dinner, and his flagon of sack (sherry) to quaff in the Mermaid Tavern on Bread Street with such cronies as Sir Walter Raleigh, Kit Marlowe, Will Shakespeare, and prominent Sea-Dogs and actors of the London theatre, while swapping tall tales of the sea.

The Plate of Brasse – We invite you to go and see for yourself Drake's historic *Plate of Brasse,* rediscovered, and now in the Bancroft Library of the University of California at Berkeley.

We hope that Queen Elizabeth II, SVCCESSOR TO HERR MAIESTY QVEEN ELIZABETH, will also come visit some day, as has her husband Prince Philip, and that she will enjoy the fine wines of California, her realm and ours . . .

If you would care for more reading about people and wine, and what it can do for your patients and your home pleasure, just fill out and mail us the coupon below.

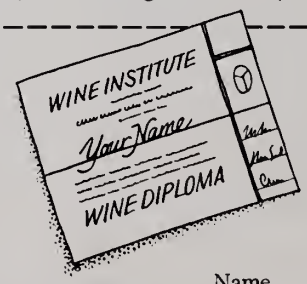
—THE WINEGROWERS OF CALIFORNIA.

HOW TO BECOME A "WINE EXPERT"

This Year We Offer to the physician, or member of his or her hospital or nursing staff or immediate family:

"WINE STUDY COURSE." Free. This is actually our 50-page, fact-filled booklet, "THE STORY OF WINE." Tells you all about wine and wine types, how made, how served, wine's fascinating history, etc. With it comes a short WINE QUESTIONNAIRE. After pleasant "studying" you quiz yourself and – if you wish – mail in your answers to us. If you pass (we're sure you will), you are a "wine expert," and to prove it we send you, also free, the little WINE DIPLOMA shown here.

"USES OF WINE IN MEDICAL PRACTICE" (A SUMMARY), also free, is our 64-page report based on recent worldwide scientific research on wine in therapy and patient care. Introduction by Russel V. Lee, M.D., noted geriatrics editor; Indications and Contraindications; Chemistry, Nutrition, Pharmacology; Wine in Hospitals and Nursing Homes; valuable Bibliography. Belongs on your bookshelf, or associate's.



WINE INSTITUTE, Dept. CM-1
717 Market Street, San Francisco, CA 94103

Kindly enroll me without cost or obligation in your famous *Wine Study Course* and send me also the free booklet *Uses of Wine in Medical Practice.* (Please print name carefully, and title, if desired, for Diploma purposes):

Name_____

Title_____

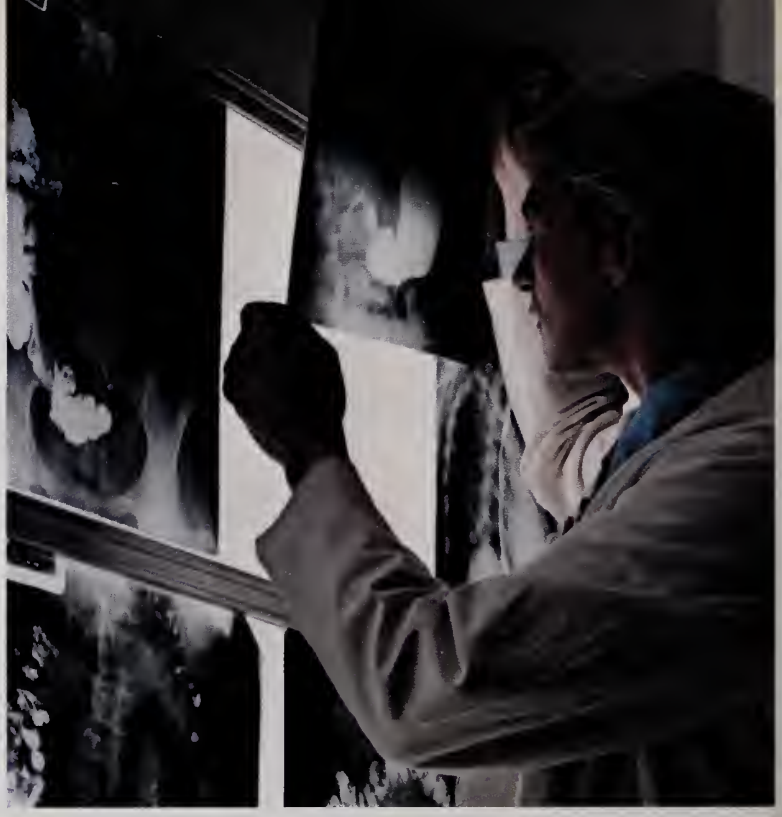
Address_____

City_____

State_____ ZIP_____

situation:
Elderly...doesn't get out much anymore...whole world slowed down.
constipation:
Poor eating habits...often, on various constipating drugs...inactive, frequently debilitated...weakened muscles ...sluggish, atonic bowel. Result—in many oldsters—constipation.
laxation:
Gentle, predictable and easy-to-take SENOKOT Tablets or Granules. Taken at bedtime, they usually induce comfortable evacuation in the morning. Leave your older patient feeling more like getting up and around.
Supplied: SENOKOT Tablets (small, easy-to-swallow)—Bottles of 50 and 100. SENOKOT Granules (delicious, cocoa-flavored)—4, 8 and 16 ounce (1 lb.) canisters.
Senokot
(standardized senna concentrate)
Tablets/Granules
a natural laxative
Purdue Frederick
A7031 128673
© COPYRIGHT 1973. THE PURDUE FREDERICK COMPANY/NORWALK, CONN. 06856

When G.I. complaints occur in the absence of organic findings, underlying anxiety may be one factor



The influence of anxiety on gastrointestinal function. Excessive anxiety and tension can adversely affect the function of any portion of the gastrointestinal system. Complaints are varied, *e.g.*, epigastric pressure, heartburn, ulcer-like pain, diarrhea, etc. A vicious circle may develop in which anxiety and G.I. disorders intensify each other.

Prime objectives of total patient therapy include: symptomatic relief, removal of apprehensions about organic disease and helping the patient understand how excessive anxiety may trigger physical

---

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions

complaints. Brief counseling and the utilization of favorable factors in the patient's personality and environment can often provide needed support.

Antianxiety therapy. Antianxiety medication may prove a valuable supplement when counseling and reassurance are not sufficient to allay the patient's emotional distress and relieve his anxiety-provoked physical complaints. The agent prescribed should be both clinically effective and generally free from undesirable side effects. Librium (chlordiazepoxide HCl) meets these requirements with a high degree of consistency, and has a wide margin of safety and an excellent record of patient acceptance. The most common side effects reported have been drowsiness, ataxia and confusion, particularly in the elderly and debilitated.

Whenever anxiety is a clinically significant factor, adjunctive Librium is used concomitantly with specific gastrointestinal drugs such as anticholinergic agents. Once anxiety has been reduced to appropriate levels, treatment with Librium should be discontinued.

For relief of excessive anxiety adjunctive

Librium® 10 mg

(chlordiazepoxide HCl)

1 or 2 capsules t.i.d./q.i.d.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc
Nutley, N.J 07110

---

in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

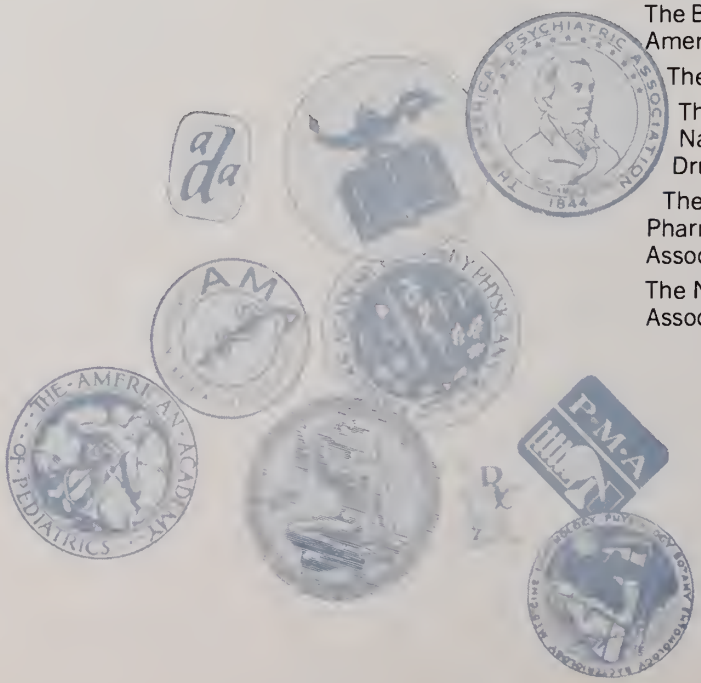
Supplied: Librium® Capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Libritabs® Tablets containing 5 mg, 10 mg or 25 mg chlordiazepoxide.

The Weight of Professional Opinion

It's time for action to defend the laws and regulations that protect your patients against drug substitution.

These professional and trade organizations are united in supporting antisubstitution statutes and regulations:

- The American Academy of Dermatology
- The Board of Directors of the American Academy of Family Physicians
- The Executive Board of the American Academy of Neurology
- The Committee on Drugs of the American Academy of Pediatrics
- The American College of Allergists
- The Executive Committee of the American College of Obstetricians and Gynecologists
- The Board of Regents of the American College of Physicians
- The Board of Trustees of the American Dental Association
- The Board of Trustees of the American Medical Association
- The American Psychiatric Association
- The Executive Committee of the National Association of Retail Druggists
- The Board of Directors of the Pharmaceutical Manufacturers Association
- The National Wholesale Druggists' Association



int Statement on Antisubstitution Laws and Regulations

The purpose of this statement is affirm the support of the participat- g organizations for the laws, regula- ns and professional traditions which ohibit the unauthorized substitution drug products.

Traditionally, physicians, den- ts and pharmacists have worked operatively to serve the best inter- s of patients. Productive coopera- in has been achieved through utual respect as well as a common ncern for the ideals of public vice. This mutual respect has been lected, in part, by joint support r the years for the adoption and orcement of laws and regulations cifically prohibiting unauthorized stitution and encouraging joint cussion and selection of the rce of supply of drug products. The basic principles of medical, den- and pharmacy practice are thus tized and preserved in the interest patient welfare.

The antisubstitution laws have obstructed enhancement of the fessional status of pharmacy any e than they have in and of them- es guaranteed absolute protec- from unsafe drugs, or freed sicians, dentists and pharmacists n their responsibilities to patients. practical matter, however, such s and regulations encourage inter- essional communications regard- drug product selection and assure n profession the opportunity to rcise fully its expertise in drug ge, to the advantage of patients.

Physicians and dentists should rged to increase the frequency regularity of their contacts with rmacists in selection of quality g products, recognizing that economies to patients can be improved through such communication, taking into account the patients' needs. The pharmacist's knowledge of the chemical characteristics of drugs, their mode of action, toxic properties and other characteristics that assist in making drug selection decisions should be utilized to the fullest extent practicable by physicians and dentists in serving their patients.

Since drug product selection entails knowledge derived from clinical experience, the physician's and dentist's roles in product selection remain primary and do not permit delegation of decisions requiring medical and dental judgments. A broader role in therapy will evolve for pharmacists as improved understanding and cooperation among the professions continue to grow.

There has been no evidence that there are convincing reasons to modify or repeal existing laws and regulations prohibiting the unauthorized substitution of another drug product for the one specified by a prescriber. It is our belief that such laws and regulations merit the joint support of the medical, dental and pharmaceutical professions and the pharmaceutical industry.

Add your opinion to the weight of other professionals and send it to your state assemblyman or legislator.

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W., Washington, D. C. 20005

When the asthmatic can anticipate the attack

Bronkotabs®

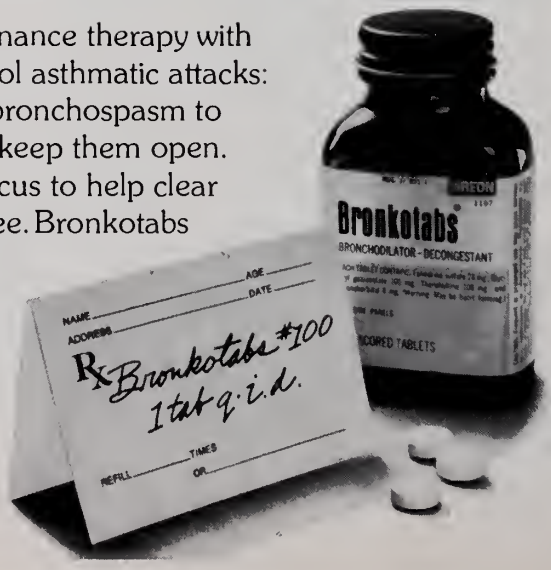
Each tablet contains ephedrine sulfate 24 mg; theophylline 100 mg; glyceryl guaiacolate 100 mg; phenobarbital 8 mg (warning: may be habit-forming).

can help forestall or relieve it

Why day to day maintenance therapy with Bronkotabs helps control asthmatic attacks:

Bronkotabs relieves bronchospasm to open airways and help keep them open.

Bronkotabs thins mucus to help clear the tracheobronchial tree. Bronkotabs decongests bronchiolar mucosa to improve the passage of air. Economical long-term therapy.



PRECAUTIONS AND ADVERSE EFFECTS: Sympathomimetic side effects are minimal, and there are none of the dangers or side effects associated with steroid therapy. However, frequent or prolonged use may cause nervousness, restlessness or sleeplessness. Should be used with caution in the presence of hypertension, heart disease or hyperthyroidism. Drowsiness may occur. Ephedrine may cause urinary retention, especially in the presence of partial obstruction, as in prostatism.

DOSAGE: Adults, one tablet every three or four hours, four or five times daily. Children over six, one-half the adult dose. Children under six, as directed.

SUPPLIED: Bottles of 100 and 1,000 tablets.

BREON

BREON LABORATORIES INC.
90 Park Avenue, New York, N.Y. 10016

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Edema associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. Also, mild to moderate hypertension.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: **Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired.** Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, descreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

Supplied: Bottles and Single Unit Packages of 100 capsules.

SK&F CO.
Carolina, P.R. 00630
Subsidiary of SmithKline Corp.

WHEN YOUR DIGITALIZED PATIENT NEEDS A DIURETIC, SHE NEEDS DYAZIDE®

- relieves edema*
- conserves potassium
- reduces the risk of digitalis intoxication due to potassium depletion. Potassium depletion sensitizes the myocardium to the toxic effects of digitalis, and reduces its inotropic effect.

Trademark

DYAZIDE®

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

MEETS THE HEARTFELT NEED OF THE DIGITALIZED PATIENT

THE NATURAL WAY

For more than thirty years PREMARIN (Conjugated Estrogen Tablets, U.S.P.) has been prepared with natural equine estrogens exclusively—without synthetic estrogen supplements. For more than thirty years it has provided the complete estrogen complex in the proportions found in its natural source. And for more than thirty years PREMARIN has enjoyed an unparalleled record of clinical efficacy and acceptance.

PREMARIN. The only estrogen preparation available that contain natural estrogens exclusively and al meets all U.S.P. specifications for conjugated estrogens. Assurance of quality for you and your patients.

PREMARIN . . . naturally.

BRIEF SUMMARY
(For full prescribing information, see package circular.)
PREMARIN®
(Conjugated Estrogens Tablets, U.S.P.)

Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.
Warnings: Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.
Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Pre-existing uterine fibromyomata may increase in size while using estrogens; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.
Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest
Dosage and Administration: PREMARIN should be administered cyclically (3 weeks of daily estrogen and 1 week off) for all indications except selected cases of carcinoma and prevention of postpartum breast engorgement.

Menopausal Syndrome—1.25 mg. daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg. to 1.25 mg. daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg. daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg. to 1.25 mg. or more daily, depending upon the tissue response of the individual patient. Administer cyclically.
How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)

No. 865—Each *purple* tablet contains 2.5 mg., in bottles of 100 and 1,000.

No. 866—Each *yellow* tablet contains 1.25 mg., in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 867—Each *red* tablet contains 0.625 mg., in bottles of 100 and 1,000.

No. 868—Each *green* tablet contains 0.3 mg., in bottles of 100 and 1,000. 7352

PREMARIN®

BRAND OF **CONJUGATED ESTROGENS TABLETS, U.S.P.**

CONTAINS ONLY NATURAL ESTROGENS ...NO SYNTHETICS OR SUPPLEMENTS

Ayerst

AYERST LABORATORIES
New York, N.Y. 10017

Part of a series on the clinical, bacteriological and pharmacological aspects of Bactrim therapy.

This is Bactrim against E. coli, Proteus

These are results from clinical trials* in which patients with chronic urinary tract infections (primarily cystitis, pyelitis and pyelonephritis), more than half with obstructive complications, were treated with Bactrim for 10 days and evaluated at intervals up to 32 days after termination of therapy. Patients were considered to have a significant bacteriological response when the urine culture revealed 10,000 or fewer colonies/ml of any single organism cultured from a midstream clean-catch specimen.

Before prescribing Bactrim, please consult complete product information for all adverse reactions, contraindications, precautions and warnings.

ROCHE

performance
spp. and Klebsiella

	Excellent initial response* after 10 days of therapy	Impressive response maintained 32 days after termination of therapy
E. coli infections	97.1% of 105 patients	73.1% of 93 patients
Proteus spp. infections	81.1% of 37 patients	60.0% of 35 patients
Klebsiella infections	85.7% of 21 patients	65.0% of 20 patients

Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley, New Jersey

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

In cystitis, pyelonephritis and pyelitis diagnosed as chronic and due to susceptible urinary tract pathogens, usually E. coli, Klebsiella-Enterobacter and Proteus mirabilis.

Please see following page for summary of product information.

In cases of cystitis, pyelonephritis and pyelitis diagnosed as chronic*

Bactrim™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

- aggressive antibacterial activity
- interrupts essential metabolic process of susceptible organisms, usually E. coli, Klebsiella-Enterobacter, P. mirabilis, and, less frequently, indole-positive proteus species
- over 91% initial efficacy in clinical studies of patients with urinary tract infection diagnosed as chronic*
- impressive response even in cases with obstructive complications
- not recommended for children under 12, during pregnancy or the nursing period
- no loading dose; two tablets b.i.d. recommended for 10-14 days

*due to susceptible organisms

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Enterobacter, Proteus mirabilis,* and, less frequently, indole-positive proteus species).

NOTE: The increasing frequency of resistant organisms limits the usefulness of antibacterials, especially in chronic and recurrent urinary tract infections.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia in elderly patients on diuretics, primarily thiazides. Sore throat, fever, pallor or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted. Data are insufficient to recommend use in infants and children under 12.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, allergy or bronchial asthma; and in those with glucose-6-phosphate dehydrogenase deficiency, where hemolysis may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for children under 12. Usual adult dosage: Two tablets b.i.d. for 10 to 14 days. For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	2 tablets every 24 hours
Below 15	Use not recommended

Supplied: Tablets, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Maybe the patient's self-diagnosis is right. He could have hay fever. But that bright red nasal mucosa, along with the thick discharge and excoriation around the nares, strongly suggests that the main problem is a cold. Hay fever or another form of allergic rhinitis may or may not be an underlying factor.

If a complete history and examination rule out allergic rhinitis, the long-term outlook will be a lot more favorable than his own "diagnosis" would have indicated.

But right now, whether he's got allergic rhinitis or a cold, he's suffering from the same irritating symptoms of drip, congestion and stuffiness. Try DIMETAPP EXTENTABS®. They're formulated to relieve these symptoms without much chance of causing drowsiness or overstimulation. Your patients will appreciate the 24-hour relief they can get from just one tablet every 12 hours.

Cold or

Allergy?

Whether it's a cold or an allergy, Dimetapp Extentabs® effectively relieve stuffiness, drip and congestion.

INDICATIONS: Dimetapp Extentabs are indicated for symptomatic relief of allergic manifestations of upper respiratory illnesses, such as the common cold, seasonal allergies, sinusitis, rhinitis, conjunctivitis and otitis. In these cases it quickly reduces inflammatory edema, nasal congestion and excessive upper respiratory secretions, thereby affording relief from nasal stuffiness and postnasal drip.
CONTRAINDICATIONS: Hypersensitivity to antihistamines of the same chemical class. Dimetapp Extentabs are contraindicated during pregnancy and in children under 12 years of age. Because of its drying and thickening effect on the lower respiratory secretions, Dimetapp is not recommended in the treatment of bronchial asthma. Also, Dimetapp Extentabs are contraindicated in concurrent MAO inhibitor therapy.
WARNINGS: *Use in children.* In infants and children particularly, antihistamines in overdosage may produce convulsions and death.
PRECAUTIONS: Administer with care to patients with cardiac or peripheral vascular diseases or hypertension. Until the patient's response has been determined, he should be cautioned against engaging in operations requiring alertness such as driving an automobile, operating machinery, etc. Patients receiving antihistamines should be warned against possible additive effects with CNS depressants such as alcohol, hypnotics, sedatives, tranquilizers, etc.
ADVERSE REACTIONS: Adverse reactions to Dimetapp Extentabs may include hypersensitivity reactions such as rash, urticaria, leukopenia, agranulocytosis, and thrombocytopenia; drowsiness, lassitude, giddiness, dryness of the mucous membranes, tightness of the chest, thickening of bronchial secretions, urinary frequency and dysuria, palpitation, hypotension/hypertension, headache, faintness, dizziness, tinnitus, incoordination, visual disturbances, mydriasis, CNS-depressant and (less often) stimulant effect, anorexia, nausea, vomiting, diarrhea, constipation, and epigastric distress.
HOW SUPPLIED: Light blue Extentabs in bottles of 100 and 500.

Dimetapp Extentabs®

Dimetane® (brompheniramine maleate), 12 mg.; phenylephrine HCl, 15 mg.; phenylpropanolamine HCl, 15 mg.

A·H·ROBINS

A. H. Robins Company, Richmond, Va. 23220

when pain goes on... and on... and on–

For the patient with a terminal illness, PAIN past, present, and future can dominate his thoughts until it becomes almost an obsession. The more he is aware of the pain he is now experiencing, the more difficult it is to erase his memory of yesterday's pain, and to allay his fearful anticipation of tomorrow's pain.

Surely the last thing this patient needs is an analgesic containing caffeine to stimulate the senses and heighten pain awareness. A far more logical choice is Phenaphen with Codeine. The sensible formula provides ¼ grain of phenobarbital to take the nervous "edge" off, so the rest of the formula can help control the pain more effectively. Don't you agree, Doctor, that psychic distress is an important factor in most of your terminal and long-term convalescent patients?

the analgesic formula that calms instead of caffeinates

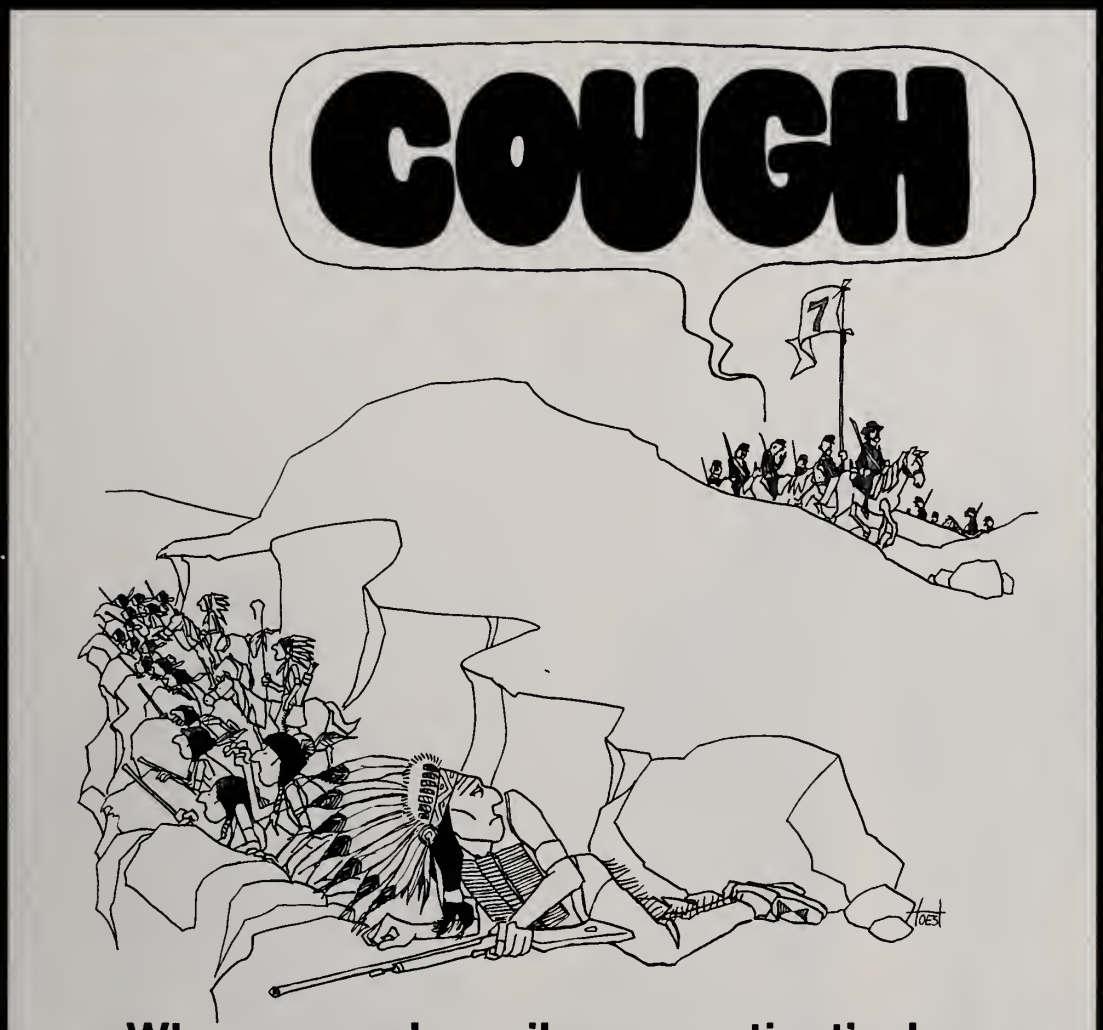
Phenaphen® with Codeine

Phenaphen with Codeine No. 2, 3, or 4 contains: Phenobarbital (¼ gr.), 16.2 mg. (warning: may be habit forming); Aspirin (2½ gr.), 162.0 mg.; Phenacetin (3 gr.), 194.0 mg.; Codeine phosphate, ¼ gr. (No. 2), ½ gr. (No. 3) or 1 gr. (No. 4) (warning: may be habit forming).

Indications: Provides relief in severer grades of pain, on low codeine dosage, with minimal possibility of side effects. Its use frequently makes unnecessary the use of addicting narcotics. **Contraindications:** Hypersensitivity to any of the components. **Precautions:** As with all phenacetin-containing products, excessive or prolonged use should be avoided. **Side effects:** Side effects are uncommon, although nausea, constipation and drowsiness may occur. **Dosage:** Phenaphen No. 2 and No. 3—1 or 2 capsules every 3 to 4 hours as needed; Phenaphen No. 4—1 capsule every 3 to 4 hours as needed. For further details see product literature.

(III) Phenaphen with Codeine is now classified in Schedule III, Controlled Substances Act of 1970. Available on written or oral prescription and may be refilled 5 times within 6 months, unless restricted by state law.

A. H. Robins Company, Richmond, Va. A·H·ROBINS



When a cough spoils your patient's day...

Triaminic® Expectorant

Each teaspoonful (5 ml.) contains:
riaminic, 25 mg. (phenylpropanolamine hydrochloride, 12.5 mg.; pheniramine maleate, 6.25 mg.; pyrilamine maleate, 6.25 mg.); glyceryl guaiacolate, 100 mg.; alcohol, 5%.

Triaminic® Expectorant with Codeine©

Each teaspoonful (5 ml.) contains:
Codeine phosphate, 10 mg. (Warning: May be habit forming); Triaminic, 25 mg. (phenylpropanolamine hydrochloride, 12.5 mg.; pheniramine maleate, 6.25 mg.; pyrilamine maleate, 6.25 mg.); glyceryl guaiacolate, 100 mg.; alcohol, 5%.

Triaminic Expectorant with Codeine is a Schedule V controlled substance.

The Adult Expectorants that are great for kids, too.

Dorsey Laboratories/Division of Sandoz-Wander, Inc./Lincoln, Nebraska 68501

to help treat what you often find:
obvious moderate to severe anxiety
with a less obvious underlying depression

TRIAVIL®

containing perphenazine and amitriptyline HCl

a tranquilizer–antidepressant

"... and she'd jump every time the phone rang."

"All right, I agree, she was obviously very anxious... you said she hadn't been sleeping..."

"She felt *tired enough* to sleep... not relaxed enough... food, too... she's too nervous to eat... says she *can't* relax... afraid there's something very wrong with her."

"... that's a good place to start. Did you find anything wrong with her?"

Treatment with TRIAVIL—a balanced view.

Tablets TRIAVIL are available in four different combinations affording flexibility and individualized dosage adjustment. Close supervision of patients is essential until satisfactory remission has taken place. Since suicide is a possibility in any depressive illness, patients should not have easy access to large quantities of the drug. The drug may impair alertness and potentiate the response to alcohol. It should not be used during the acute recovery phase following myocardial infarction or given to patients who have received an MAOI within two weeks. TRIAVIL should be used with caution in glaucoma and in patients prone to urinary retention. It is contraindicated in CNS depression and in the presence of evidence of bone marrow depression.

MSD MERCK SHARP DOHME

For a brief summary of prescribing information, please turn to the following page.

ot a thing... negative... nothing
ganically wrong. Still has a
ir list of somatic complaints.
e tried to reassure her... to let
r talk... to help her sort things
t. She's been in to see me a
mber of times."

"...what about medication?"

"Just what I was coming to...
I've had her on tranquilizers.
And *that's* what puzzles me. I'm
not getting the response I hoped
for. She's no better... perhaps a
little worse. It's sad to see."

"...I think *'sad'* may be what
you're not seeing! You know,
this sounds like another case
where the *anxiety* is so clear and
pervasive we tend to overlook
the depressive part of the picture.
I'm not sure that we shouldn't
almost always think of anxiety
with depression... not anxiety
alone. Take another look at your
records... talk to her some more.
If you decide she's depressed,
I think you might want to
consider TRIAVIL.... It can help
relieve her entire symptom
complex... control the anxiety...
while at the same time treat
the depression."

TRIAVIL®

to help treat what you often find:
obvious moderate to severe anxiety
with a less obvious underlying depression

containing perphenazine and amitriptyline HCl

a tranquilizer–antidepressant

Available:
TRIAVIL® 2-25: Each tablet contains
2 mg. perphenazine and 25 mg. amitriptyline HCl

TRIAVIL® 2-10: Each tablet contains
2 mg. perphenazine and 10 mg. amitriptyline HCl

TRIAVIL® 4-25: Each tablet contains
4 mg. perphenazine and 25 mg. amitriptyline HCl

TRIAVIL® 4-10: Each tablet contains
4 mg. perphenazine and 10 mg. amitriptyline HCl

INITIAL THERAPY FOR MANY PATIENTS
TRIAVIL® 2-25 (or TRIAVIL® 4-25) t.i.d. or q.i.d.

FOR FLEXIBILITY IN ADJUSTING MAINTENANCE THERAPY
TRIAVIL® 2-10 (or TRIAVIL® 4-10)

CONTRAINDICATIONS: Central nervous system depression from drugs (barbiturates, alcohol, narcotics, analgesics, antihistamines); bone marrow depression; known hypersensitivity to phenothiazines or amitriptyline. Do not give concomitantly with MAOI drugs because hyperpyretic crises, severe convulsions, and deaths have occurred from such combinations. Allow minimum of 14 days between therapies, then initiate therapy with TRIAVIL cautiously, with gradual increase in dosage until optimum response is achieved. Not recommended for use during acute recovery phase following myocardial infarction.

WARNINGS: TRIAVIL should not be given with guanethidine or similarly acting compounds. Use cautiously in patients with history of urinary retention, angle-closure glaucoma, increased intraocular pressure, or convulsive disorders. Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressants, including amitriptyline HCl, particularly in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of conduction time. Myocardial infarction and stroke have been reported with tricyclic antidepressant drugs. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. Caution patients performing hazardous tasks, such as operating machinery or driving motor vehicles, that drug may impair mental and/or physical abilities. Not recommended in children or during pregnancy.

PRECAUTIONS: Suicide is a possibility in depressed patients and may remain until significant remission occurs. Such patients should not have access to large quantities of this drug.

Perphenazine: Should not be used indiscriminately. Use with caution in patients who have previously exhibited severe adverse reactions to other phenothiazines. Likelihood of untoward actions is greater with high doses. Closely supervise with any dosage. The antiemetic effect of perphenazine may obscure signs of toxicity due to overdosage of other drugs or make more difficult the diagnosis of disorders such as brain tumor or intestinal obstruction. A significant, not otherwise explained, rise in body temperature may suggest individual intolerance to perphenazine, in which case discontinue.

If hypotension develops, epinephrine should not be employed, as its action is blocked and partially reversed by perphenazine. Phenothiazines may potentiate the action of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) and atropine. In concurrent therapy with any of these, TRIAVIL should be given in reduced dosage. May also potentiate the action of heat and phosphorous insecticides.

Amitriptyline: In manic-depressive psychosis, depressed patients may experience a shift toward the manic phase if they are treated with an antidepressant. Patients with paranoid symptomatology may have an exaggeration of such symptoms. The tranquilizing effect of TRIAVIL seems to reduce the likelihood of this effect. When amitriptyline HCl is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with 1 g of ethchlorvynol and 75-150 mg of amitriptyline HCl.

Amitriptyline HCl may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

Concurrent administration of amitriptyline HCl and electroshock therapy may increase the hazards associated with such therapy. Such treatment should be limited to patients for whom it is essential. Discontinue several days before elective surgery if possible. Elevation and lowering of blood sugar levels have both been reported.

ADVERSE REACTIONS: Similar to those reported with either constituent alone.

Perphenazine: Side effects may be any of those reported with phenothiazine drugs: extrapyramidal symptoms (opisthotonus, oculogyric crisis, hyperreflexia, dystonia, akathisia, acute dyskinesia, ataxia, parkinsonism) can usually be controlled by the concomitant use of effective antiparkinsonian drugs and/or by reduction in dosage, but sometimes persist after discontinuation of the phenothiazine.

Tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy with phenothiazines and related agents has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Involuntary movements of the extremities sometimes occur. There is no known treatment for tardive dyskinesia; antiparkinsonism agents usually do not alleviate the symptoms. It is advised that all antipsychotic agents be discontinued if the above symptoms appear. If treatment is reinstituted, or dosage of the particular drug increased, or another drug substituted, the syndrome may be masked. It has been suggested that fine vermicular movements of the tongue may be an early sign of the syndrome, and that the full-blown syndrome may not develop if medication is stopped when lingual vermiculation appears.

Other side effects are skin disorders (photosensitivity, itching, erythema, urticaria, eczema, up to exfoliative dermatitis); other allergic reactions (asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions); peripheral edema; reversed epinephrine effect; hyperglycemia; endocrine disturbances (lactation, galactorrhea, gynecomastia, disturbances of menstrual cycle); altered cerebrospinal fluid proteins; paradoxical excitement; hypertension, hypotension, tachycardia, and ECG abnormalities (quinidine-like effect); reactivation of psychotic processes; catatonic-like states; autonomic reactions, such as dry mouth or salivation, headache, anorexia, nausea, vomiting, constipation, obstipation, urinary frequency or incontinence, blurred vision, nasal congestion, and a change in pulse rate; hypnotic effects; pigmentary retinopathy; corneal and lenticular pigmentation; occasional lassitude, muscle weakness, mild insomnia. Other adverse reactions reported with various phenothiazine compounds include blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia); liver damage (jaundice, biliary stasis); grand mal convulsions, cerebral edema; polyphagia; photophobia; skin pigmentation; and failure of ejaculation.

Amitriptyline: Note: Listing includes a few reactions not reported for this drug, but which have occurred with other pharmacologically similar tricyclic antidepressant drugs. *Cardiovascular:* Hypotension; hypertension; tachycardia; palpitation; myocardial infarction; arrhythmias; heart block; stroke. *CNS and Neuromuscular:* Confusional states; disturbed concentration; disorientation; delusions, hallucinations; excitement; anxiety; restlessness; insomnia; nightmares; numbness, tingling, and paresthesias of the extremities; peripheral neuropathy; incoordination; ataxia; tremors; seizures; alteration in EEG patterns; extrapyramidal symptoms; tinnitus. *Anticholinergic:* Dry mouth; blurred vision; disturbance of accommodation; constipation; paralytic ileus; urinary retention; dilatation of urinary tract. *Allergic:* Skin rash; urticaria; photosensitization; edema of face and tongue. *Hematologic:* Bone marrow depression including agranulocytosis; leukopenia; eosinophilia; purpura; thrombocytopenia. *Gastrointestinal:* Nausea; epigastric distress; vomiting; anorexia; stomatitis; peculiar taste; diarrhea; parotid swelling; black tongue. *Endocrine:* Testicular swelling and gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido; elevated or lowered blood sugar levels. *Other.* Dizziness, weakness; fatigue; headache; weight gain or loss; increased perspiration; urinary frequency; mydriasis; drowsiness; jaundice; alopecia. *Withdrawal Symptoms:* Abrupt cessation after prolonged administration may produce nausea, headache, and malaise. These are not indicative of addiction.

OVERDOSAGE: Treatment is symptomatic and supportive. However, the intravenous administration of 1-3 mg of physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. On this basis, in severe overdosage with perphenazine-amitriptyline combinations, symptomatic treatment of central anticholinergic effects with physostigmine salicylate should be considered.

For more detailed information, consult your MSD Representative or see full Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486.

MSD
MERCK SHARP & DOHME

Case history #4

Charles' well-being comes first.

Charles' being well comes first.

In September 1968, while working as a driver/salesman for a Sacramento beverage company, Charles Foster's automobile overturned. He was thrown from the car and sustained a number of serious injuries, including a compression fracture of the vertebrae with cord injury, making him paraplegic.

During Charles' initial period of intensive care, State Fund cooperated with his doctors, setting up a long-range program of health care. Charles suffered a cardiac arrest during spinal surgery, but he was successfully resuscitated and continued to improve. After leaving the hospital, he entered the Kaiser Foundation Rehabilitation Center in Vallejo, where he quickly learned to adapt to his paralysis.

State Fund's rehabilitation staff visited Charles regularly to help him plan his new life. They helped him buy a specially equipped car to drive to and from school and arranged and paid for home alterations to accommodate his wheelchair and his impairment.

In 1973, Charles Foster took advantage of State Fund's *Therapeutic Capitalization* Program, enabling him to receive a lump-sum payment for the total projected cost of his lifetime medical and living expenses, which he invested in secure mutual funds and in a business of his own. Today, Charles is teamed with another paraplegic, and together they operate The Wheelchair Boutique, specializing in sales, repair, and rental of hospital equipment.

Charles has come a long way since his accident, with courage and determination—and the help of State Fund.

Conserving your human resources is our only business

STATE COMPENSATION INSURANCE FUND

Must vasodilators and therapy for other diseases come into conflict?

not if the vasodilator is

VASODILAN®

(ISOXSUPRINE HCl)

the compatible vasodilator... no treatment conflicts reported

The cerebral or peripheral vascular disease patient often has coexisting disease[1] which calls for another drug along with his vasodilator. It may be a hypoglycemic, miotic, antihypertensive, diuretic, anticoagulant, corticosteroid, or coronary vasodilator.

Vasodilan is not incompatible with any of these drugs—no treatment conflict has been reported. And, unlike other vasodilators, Vasodilan has not been reported to affect carbohydrate metabolism, liver function, or intraocular pressure—or to complicate treatment of diabetes, hypertension, peptic ulcer, glaucoma, or liver disease.

In fact, there are no known contraindications to the use of Vasodilan in recommended oral doses, other than that it should not be given in the presence of frank arterial bleeding or immediately postpartum.

1. Gertler, M. M., et al.: Geriatrics *25*:134-148 (May) 1970.

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.
3. Threatened abortion.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.

Dosage and Administration: 10 to 20 mg. three or four times daily.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

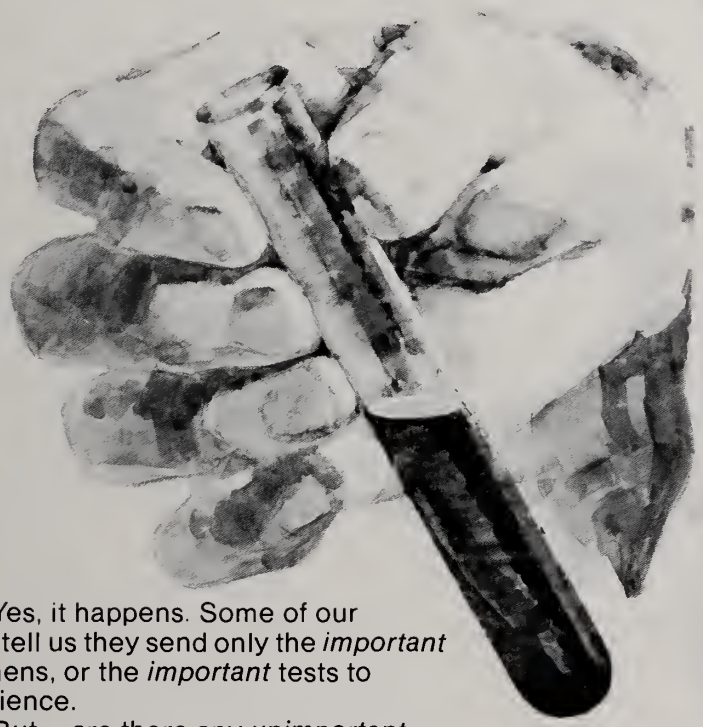
Adverse Reactions: On rare occasions, oral administration of the drug has been associated in time with the occurrence of severe rash. When rash appears, the drug should be discontinued. Occasional overdosage effects such as transient palpitation or dizziness are usually controlled by reducing the dose.

Supplied: Tablets, 10 mg.—bottles of 100, 1000, 5000 and Unit Dose; 20 mg.—bottles of 100, 500 and Unit Dose.

© 1973 MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA 47721 U.S.A. 734017

Mead Johnson LABORATORIES

"Send it out to Bio-Science. It's important."



Yes, it happens. Some of our clients tell us they send only the *important* specimens, or the *important* tests to Bio-Science.

But...are there any *unimportant* patients? Of course not. If a test is worth running at all, if a result is worth entering in the chart, it's worth the best care and attention you can get from a referral laboratory—and that means sending it to Bio-Science.

Whether sent to our Main Laboratory in Van Nuys, or to our Branch Laboratories in Philadelphia or in New York, you are assured of the same quality control, the same methods, the same normals—all backed by the name and reputation of Bio-Science Laboratories.

Bio-Science Laboratories

Main Lab: 7600 Tyrone Ave., Van Nuys, California 91405

Philadelphia Branch: 116 So. Eighteenth St., Philadelphia, Pa. 19103

New York Branch: 5 Nassau St., Rockville Centre, N.Y. 11570

Bio-Science Laboratories
7600 Tyrone Avenue
Van Nuys, California 91405 Dept. BB

5 Nassau St.,
Rockville Centre, N.Y. 11570

116 So. Eighteenth St.,
Philadelphia, Pa. 19103

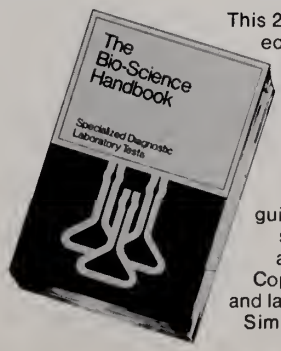
Gentlemen: Please send me, without obligation:
- ☐ A copy of your Handbook of Specialized Diagnostic Laboratory Tests
- ☐ A lab pack containing a small supply of postage-paid mailing containers and Fee Schedule

Name _____

Address _____

City _____ State _____ Zip _____

FREE
HANDBOOK OF SPECIALIZED DIAGNOSTIC LABORATORY TESTS



This 200-page book, now in its tenth edition, is a uniquely informative source to keep you up-to-date on the newer laboratory tests, many of which are not yet in the textbooks, but are now available to all clinicians from Bio-Science Laboratories. You will find it a handy reference guide for normal values and quick summations on tests which can aid in your diagnostic problems. Copies are available to physicians and lab personnel without obligation. Simply fill out and mail this coupon.

IN GONORRHEA

INJECTION

Wycillin®

(STERILE PROCAINE PENICILLIN G SUSPENSION) WYETH

Gonorrhea, according to the national Center for Disease Control, is, if the parenteral route is chosen, most effectively treated with aqueous procaine penicillin G. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given at least 30 minutes prior to injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reaction.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings.")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated)—Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, preferably given at least 30 minutes prior to injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units. I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million units daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each TUBEX® disposable syringe 2,400,000 units (4-cc. size) contains procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.7% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. The multiple-dose 10-cc. vial contains per cc. 300,000 units procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. polyvinylpyrrolidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population.* And growing.

Among those in the 20-24 age-group, the incidence is even higher. And it, too, is growing.

In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

IN SYPHILIS
INJECTION
Bicillin® LONG-ACTING
(STERILE BENZATHINE PENICILLIN G SUSPENSION) WYETH

Syphilis is preferably treated with benzathine penicillin G, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular benzathine penicillin G.—Venereal infections: Syphilis, yaws, bejel and pinta.

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: 2,400,000 units in 4-cc. single dose disposable syringe. Each TUBEX disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. Units benzathine penicillin G (as active ingredient); 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. polyvinylpyrrolidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Wyeth Laboratories
Philadelphia, Pa. 19101

U S Dept. of Health, Education, and Welfare: VD Fact Sheet 1972. Publication No. (HSM) 73-8195.

Our prescription for your practice: Take MediManager and get plenty of sleep.

Security Pacific Bank is glad to introduce MediManager: A comprehensive financial management package for the physician and dentist.

MediManager is the most complete professional service package ever offered to physicians and dentists. It's designed to be of help in (1) patient billing and collection, (2) patient credit, (3) equipment financing, (4) acquisition of facilities, and (5) estate management.

MediManager features a computerized patient billing service with insurance form preparation capabilities. It offers remittance banking and payroll help, as well as a unique patient credit plan that gives you prompt payment for your services. MediManager provides commercial and real estate loans, equipment loans and leasing, auto leasing and locational assistance. Finally, it can help you with trusts, pension plans and profit-sharing programs.

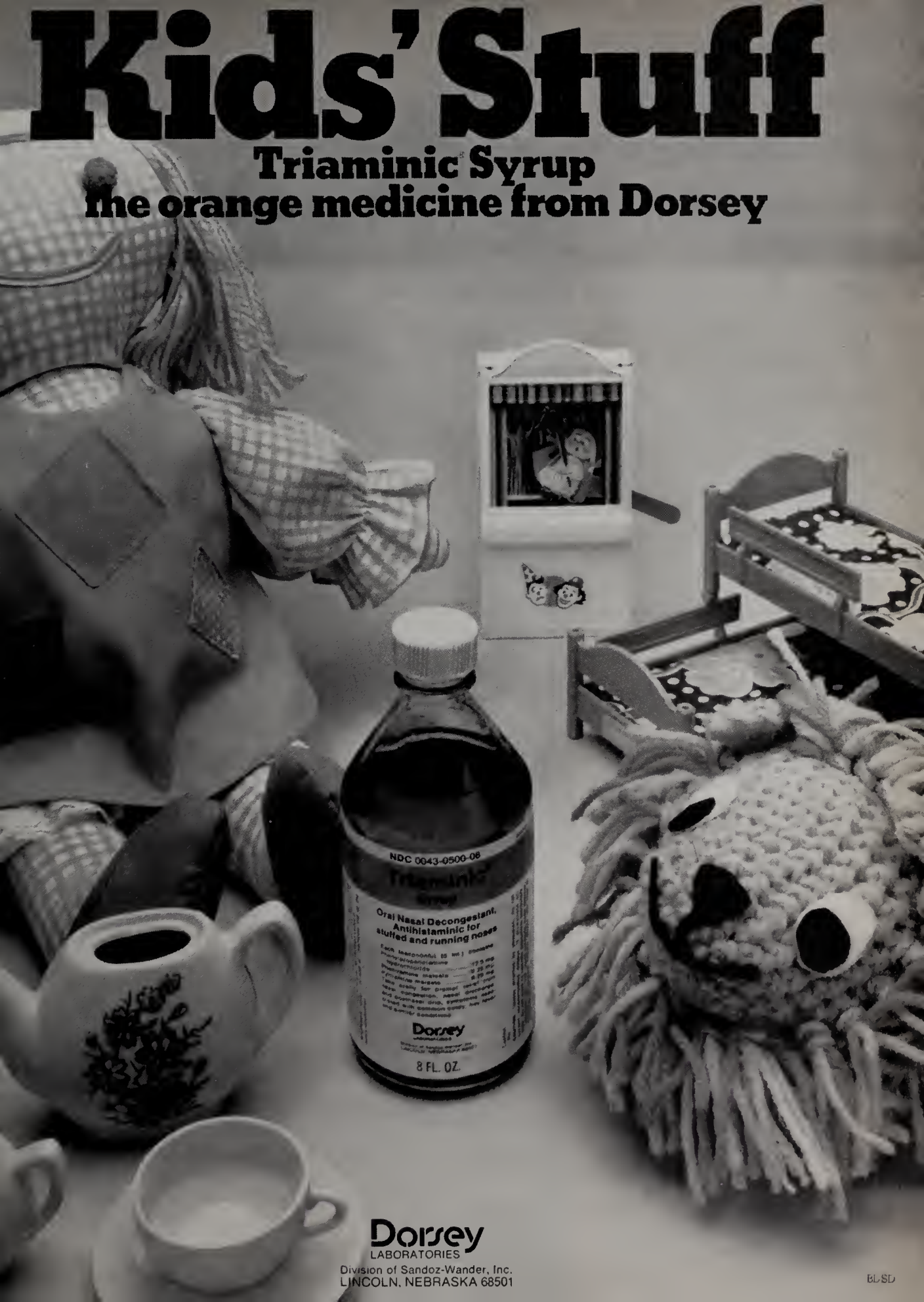
Ask your branch manager about MediManager: Something special from Security Pacific Bank.

SECURITY PACIFIC BANK
SOMETHING SPECIAL

©1973 SECURITY PACIFIC NATIONAL BANK MEMBER FDIC

Kids' Stuff

Triaminic® Syrup
the orange medicine from Dorsey



Dorsey
LABORATORIES
Division of Sandoz-Wander, Inc.
LINCOLN, NEBRASKA 68501

BL-SD

Classified Advertisements

The rate for each insertion is **$2.50 per line** (average six words per line) **with five line minimum.**

Box number charge: $1.50 each month.

Classified display rates $25.00 per inch.

Copy for classified advertisements should be received not later than **the fifth of the month preceding issue.** • Classified advertisers using Box Numbers forbid the disclosure of their identity. Your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the rules of the Advertising Committee.

CLASSIFIED ADVERTISEMENTS ARE PAYABLE IN ADVANCE

PHYSICIANS WANTED

INTERNIST, GENERALIST AND UROLOGIST, State Veterans Home and Hospital. Salary depending upon training, experience and position to be filled. Excellent retirement plan and other benefits. Located one hour from San Francisco In beautiful Napa Valley. Call or write John P. Preston, Administrator, Phone (707) 944-2422.

SACRAMENTO, CALIF.—SACRAMENTO COUNTY: The School of Medicine and the Sacramento Medical Center of the University of California, Davis, are seeking a qualified physician to direct an active hospital emergency department at its large metropolitan university medical center located in Sacramento, California. The successful candidate will be expected to develop a residency training program in emergency medicine as well as an academic program within the School of Medicine in the area of emergency medicine. The applicant should have prior experience in an emergency room setting and qualifications which would merit an appointment to an academic position within the University of California. Certification by one of the specialty boards is required. While this certification might be in surgery or internal medicine, other specialty board certifications will be considered. The salary range will be consistent with the level of academic appointment. Interested persons may contact Mrs. Wanda Kennedy, Personnel Office, School of Medicine, University of California, Davis, CA 95616, at area code (916) 752-0331 or 752-0327. WE ARE AN EQUAL OPPORTUNITY EMPLOYER; MINORITY APPLICANTS ENCOURAGED.

RESIDENCIES & INTERNSHIPS—BAKERSFIELD, KERN COUNTY: Accepting applications for 1975-76. First year residencies in fully approved four year clinically oriented program (non pyramid). Applicants requiring one or more years of General Surgery for sub-specialty welcome. Full patient responsibility, supervision by full-time Board Certified General and Thoracic Chairman and Associate Director, with full-time Board Certified Neurosurgeon, Urologist and Anesthesiologist. Board Certified attending staff in plastic and ortho surgery. Salary $13,080 annually; meals. Must be eligible for California license. Contact: Chairman, Department of Surgery, Kern General Hospital, 1830 Flower Street, 93305. Phone (805) 323-7651, ext. 214.

LOS ANGELES—ORANGE COUNTIES. Growing HMO needs more General Practitioners, Pediatricians, Orthopods, OB/GYN's and Internist. Competitive salaries, regular increases and tax-sheltered fringe benefits. Two newly opened medical centers. Send your curriculum vitae to: Frank Eaton, MD, Medical Director, Family Health Program, Room 4419, 2925 Palo Verde, Long Beach, CA 90815.

ALLERGIST with large interesting practice in Pasadena needs full time associate to take over bulk of practice. Retirement in view. Good income. Phone: (213) 792-4171 or 796-7487.

PHYSICIANS WANTED

WANTED FOR COMPREHENSIVE SIX-MAN expanding medical care corporation—Family Practitioner and Internist. Small, friendly city with big-city advantages; two colleges, close to Los Angeles, San Francisco, Las Vegas, ocean, mountains. All sports, four-day week, every seventh week-end on call. Good salary first year. Permanent corporation membership after first year. Write to M. E. Baurer, MD, Manor Medical Group, Inc., 223 China Grade Loop, Bakersfield, CA 93308.

PROGRESSIVE RURAL GROUP PRACTICE—Located in the Salinas Valley near MONTEREY and CARMEL has an immediate need for two Family Practitioners and an Internist (Generalist) to join an established 9-man group practice, plus 11 consultants, incorporated in 1970. Competitive starting salary and top fringe benefits. Brochure by return mail. Please call or send C.V. to: DUANE F. HYDE, MD, Southern Monterey County Medical Group (A Professional Corporation), 210 Canal St., King City, CA 93930, Tel. (408) 385-5471.

UNEXPECTED OPENING for Third Year Residency Position in General Surgery Available Now; Fourth Year (Senior) Opening July 1, 1974 in Fully Approved 4-Year Program. California License Required. Box 9377, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

FAMILY PHYSICIAN to join 2 GPs in small inc. GP in desert community. Population 20,000 near Palm Springs, California. Guarantee $50,000 minimum annual and up, prefer full-time, permanent MD. Fine residential community, outdoor sports, plenty of time off, corporate benefits. Donald A. Miller, MD, Desert Family Physicians Medical Group, 82420 Miles Ave., Indio, CA 92201, (714) 347-0648.

EMERGENCY ROOM PHYSICIAN wanted part-time or full-time for E.R. in informal community hospital in desert near Palm Springs. 20,000 population. Salary by hour or month. Plenty of time off to enjoy outdoor sports, recreation. Beautiful climate and residential community, benefits. Donald A. Miller, MD, Desert Family Physicians Medical Group, 82420 Miles Ave., Indio, CA 92201, (714) 347-0648.

EMERGENCY ROOM DIRECTOR, 100-bed hospital, desert community, population 20,000, near Palm Springs. Must be experienced in emergency medicine. Reasonable hours, plenty of time off to enjoy outdoor recreation available here, excellent salary, benefits. Donald A. Miller, MD, Desert Family Physicians Medical Group, 82420 Miles Ave., Indio, CA 92201 (714) 347-0648.

FAMILY PHYSICIAN, GP OR INTERNIST wanted to manage hospital patients of small medical group, community population 20,000 near Palm Springs. Hospital work 4 to 5 days weekly, some E.R. work, plenty of time off, guaranteed minimum, benefits, beautiful area and climate. Donald A. Miller, MD, Desert Family Physicians Medical Group, 82420 Miles Ave., Indio, CA 92201, (714) 347-0648.

SPANISH-SPEAKING PHYSICIAN GP for small desert community, family practice, part-time or fulltime positions in small medical group, excellent salary, benefits. Beautiful climate, living conditions near Palm Springs. Donald A. Miller, MD, Desert Family Physicians Medical Group, 82420 Miles Ave., Indio, CA 92201 (714) 347-0648.

GYNECOLOGIST-OBSTETRICIAN WANTED to join small medical group in desert community, population 20,000 near Palm Springs, beautiful climate, recreation. Excellent guarantee and corporate benefits. Donald A. Miller, MD, Desert Family Physicians Medical Group, 82420 Miles Ave., Indio, CA 92201 (714) 347-0648.

(Continued on Page 45)

SITUATIONS WANTED

GENERAL SURGEON, age 58, wants to relocate in Southern California. Willing to do ER work, general practice and general surgery. Author of textbook and 100 publications. Write Box 9378, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GENERAL SURGEON age 30—university trained seeks group or partnership also interested part-time university. Box 9379, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INTERNIST—Board eligible, 31, completing military September 1974. Wishes to join group or associate in Northern California. Experienced in general medicine and has some cardiology training. California license. Contact: John P. Prusmack, MD, Department of Medicine, 130th Station Hospital, APO NY 09102.

NEPHROLOGIST WANTED

NEPHROLOGIST WANTED: A one bed chronic and acute dialysis unit located in southern California in a multiservice hospital. Has an immediate need for a medical director. Located outside Los Angeles County, excellent schools, housing and continuing education opportunities in a university sponsored program. Reply to Los Alamitos Medical Investment Company, 3751 Katella Ave., Los Alamitos, CA 90720.

LOCUM TENENS WANTED

WELL QUALIFIED INTERNIST to assume active referral hospital and office practice: preferably for 4 weeks, beginning May 27, but arrangements are flexible. Five-day week, with minimum guarantee of $750 per week, and potential for more. Permanent association possible. Telephone collect (209) 723-1069 any afternoon for details.

PHYSICIANS

Employee Health Service needs Physicians—full time, days only. Calif. license required.

Contact: **THEODORE GREENBURG, MD**
LAC/USC Medical Center, Box 273
1200 N. State St., Los Angeles, Calif. 90033
(213) 225-3115, Ext. 71777

UNIVERSITY OF CALIFORNIA, SAN DIEGO

Assistant Adjunct Professor of

Surgery/Otolaryngology

Salary: $25,840

Duties will consist of providing medical consultation in head and neck surgery for graduate and postgraduate students; teaching basic science courses in anatomy, physiology, and biochemistry to above students. Conducting basic research in head and neck surgery, and supervising the research students in this field.

Candidate must be board eligible in the American Board of Otolaryngology and have special training in anatomy and physiology of the head and neck. Candidate must also have background in experimental surgery of the head and neck.

ADDRESS REPLIES TO:

ALAN NAHUM, MD
Head, Division of Otolaryngology
University Hospital, AID No. 8104
225 W. Dickinson Street
San Diego, California 92103

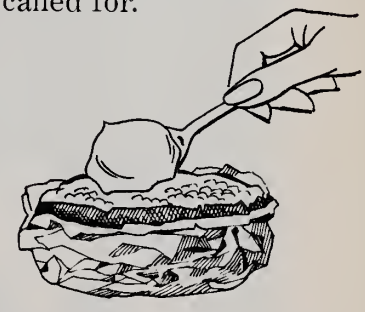
"AN EQUAL OPPORTUNITY/AFFIRMATIVE ACTION EMPLOYER"

Good news for saturated fat watchers...

ew Matey® Sour Dressing. Low in saturated fat, Cholesterol free!

Imagine. A sour dressing you can feel free to recommend. One that gives all the satisfaction of the one you had to restrict, but that has a relative saturated fat to total fat of only 18% as compared to over 50% for dairy sour cream. What's more, delicious new Matey® Non-Dairy Lo Saturate Sour Dressing is made from a blend of liquid safflower and soybean oils (the only one that is) and is *completely cholesterol free.*

If your patients are bored with a saturated fat restricted diet, they'll love the way new Matey can liven up their menu. Great for dips, on baked potatoes, fruit salad or cooking ...anywhere a sour dressing is called for.



New Matey. You'll find it in your grocer's dairy case now. Better yet, write for a free supply of coupons so you and your patients can sample it free. We'll also send you a complete data sheet for your files.

Presto Food Products, Inc.
Box 21908,
Los Angeles,
Calif. 90021

Made by the makers of Mocha Mix®...the non-dairy creamer that's lowest in saturated fat. Both available in larger sizes for hospitals and institutions.

new

DARVOCET-N®

50 mg. propoxyphene napsylate
and 325 mg. acetaminophen

Lilly TABLETS

Additional information available to the profession on request.
Eli Lilly and Company, Indianapolis, Indiana 46206

300104

THE WESTERN
Journal of Medicine

Refer to: Kasper CK, Parton L: Reproduction in hemophilia. West J Med 120:273-277, Apr 1974

Reproduction in Hemophilia

CAROL K. KASPER, MD
LANCE PARTON, BS
Los Angeles

Patterns of marriage and parenthood were studied in the families of 250 patients with severe hemophilia. The incidence of marriage among adult hemophiliacs was 82.5 percent that of age-matched males of the general United States population, as of 1968. Married hemophiliacs 30 years old or older had an average of 2.1 children each, as of 1971. In the periods 1950-1954 and 1960-1964, the numbers of children sired by hemophiliacs were 25 and 38 percent, respectively, of the numbers expected of age-matched men of the general United States population. This indicates a lesser ability or willingness to have children. The number of additional births to women who were already mothers of hemophiliacs was compared with that expected for women of the general population of the United States, matched for age and parity. In the years 1940 through 1954, the birthrates for the two groups were similar. However, in the years 1955-1968, the birthrate among carriers declined more rapidly than that in the general population. The improved medical treatment of hemophilia has apparently not resulted in a greater willingness of affected persons to transmit the defective gene.

THE MODE OF INHERITANCE of hemophilia as a sex-linked trait is well known. Given the seriousness of the disease, the suffering and expense for the patient and his family, and the expense to society through subsidized benefits, one might assume that those persons at great risk of transmitting the defective gene would refrain from parenthood. Such an assumption would be naive. Discombe[1] warned that society might soon bear sharply increased burdens because persons with hemophilia and other serious but treatable sex-linked or dominant genetic disorders were surviving to adulthood and having children, thereby rapidly increasing the number of affected persons in the population. His comments were angrily attacked in three London newspapers[2-4] by the Haemophilia Society. Members of that society argued that the decision to have children was entirely the private affair of the individual and pointed out that many hemophiliacs felt that they themselves had weathered the disease well enough, and so should their hemophiliac descendants.

The treatment for hemophilia has become far

From the Department of Medicine, University of Southern California School of Medicine, and Orthopaedic Hospital, Los Angeles. (The Orthopaedic Hospital is an International Hemophilia Training Center.)

Supported in part by Social and Rehabilitative Services, DHEW, Grant RT 18.

Reprint requests to: C. K. Kasper, MD, 2400 South Flower Street, Los Angeles, CA 90007.

more effective and convenient in the last decade with the introduction of clotting-factor concentrates and home infusion programs. The cost of treating the disease, an average of $5,000 per patient per year in Southern California, is now being borne more by government agencies or large group-insurance plans than by the individual family. The burden on the patient and family, though still great, has lessened.

We wondered whether the improved chances for the survival and well-being of hemophiliacs has led to a greater willingness to transmit the defect, and we had access to an unusually large group of hemophiliacs who were registered for care at Orthopaedic Hospital. We determined the number of children sired by hemophiliacs and the number born to women who have already had at least one hemophiliac son, and attempted to make comparisons with birthrates of the general population of the United States.

Methods

Family histories were obtained by personal interview from nearly all the patients with severe hemophilia registered at Orthopaedic Hospital as of 1971. Of these patients, 193 had severe hemophilia A and 57 had severe hemophilia B. As a part of the routine examination, information was obtained about the patient's birthdate, marital status, the birthdates and sex of his children, the birthdates and sex of his siblings (living and dead), the birthdate of his mother, the presence of hemophilia in any other relative, and the religion of the family. Patients were excluded from the survey only if no useful information was available. For example, adopted hemophiliac children were not included if we had no information about their biologic relatives.

The incidence of hemophilia appears to be similar in all racial, ethnic, religious and socioeconomic groups. The care of hemophiliacs in Southern California is heavily concentrated at Orthopaedic Hospital, with no obvious intentional or unintentional selection for or against any population group. Patients from rural and urban areas are proportionally represented. We feel that the study group is a fair sample of the general Southern California population with regard to these characteristics. For the purposes of the study, we have compared the study group to the general United States population despite the realization that the proportion of certain ethnic groups, notably Mexican-Americans, in Southern California differs from that in the general United States population.

Vital statistics publications of the federal Public Health Service provided data on the incidence of marriage by American males and birthrates for American women through the years 1940-1968, and data on the numbers of children sired by American men for most years from 1940 through 1966.

In order to compare our statistics on the number of children sired by hemophiliacs, and the number born to mothers of hemophiliacs, with the available information about the general United States population, we made the following tallies. We counted the number of hemophiliac men alive each year from 1940 through 1944, 1950 through 1954, and 1960 through 1964 and grouped this information according to their ages within the range of 15 to 44 years. We then counted the number of children sired by these men in each age and calendar-year category. From the vital statistics tables, we calculated the number of children which would have been expected for an equal number of men of the general population in each age and calendar-year category. We also counted the number of mothers of hemophiliacs alive in each year from 1940 through 1968 and grouped this information according to their ages within a selected range of 20 to 39 years and according to their parity within a selected range of one to four. Then we counted the number of births to these women in each age, parity and calendar-year category. From the vital statistics tables we calculated the number of births which would have been expected of an equal number of women of the general population in each age, parity and calendar-year category. The observed incidence of children sired by hemophiliacs and of children born to mothers of hemophiliacs was compared with the expected incidence of births, based on the vital statistics data, by means of chi-square tests.

Results

Hemophiliac Men

In Table 1 the actual incidence of marriage by hemophiliac men is compared with that expected for equal numbers of age-matched men of the general population of the United States for the year 1968. This is the most recent year for which vital statistics are available. At that time, 58 percent of hemophiliacs 20 years old or older and 75

percent of hemophiliacs 30 years old or older were married. The over-all incidence of marriage by hemophiliacs was 82 percent of that expected for age-matched males of the country's population in general.

As of 1971, 81 married hemophiliacs had a total of 130 children, of whom 59 were daughters. Of these obligatory carriers, 27 were in the child-bearing ages of 15 to 34 years old and 32 were younger than 15 years old. Married hemophiliacs born before 1940 had an average of 2.1 children each as of 1971.

In Table 2 we compare the numbers of children sired by hemophiliacs (married and unmarried) in the years 1940 to 1944, 1950 to 1954 and 1960 to 1964 with those expected for an equal number of age-matched men of the general United States population. The number of children sired by hemophiliacs was 80 percent of that for the general male population in the years 1940-1944 (an insignificant difference). However, from 1950 to 1954 and 1960 to 1964 the numbers of children were 25 and 38 percent, respectively, of those expected for the general population (a significant difference). In the latter two periods the difference between actual and expected numbers of children was most significant ($p = <0.01$) for men aged 20 to 29 years. This difference decreased in significance with increasing age.

TABLE 1.—*Comparison of Incidence of Marriage, as of 1968, for Hemophiliacs, with That Expected for Equal Numbers of Age-Matched Men of the General United States Population*

Age group, years	*Total number of hemophiliacs*	*Actual number married*	*Expected number married*	
14-19	63	3	2	
20-24	42	14	19	$p = <0.50$
25-29	38	22	29	$p = <0.01$
30-34	21	15	18	$p = <0.10$
35-44	27	18	24	$p = <0.01$
45-54	11	10	10	
55-64	5	5	4	
Total age 14-64	207	87	106	$p = <0.01$

Mothers of Hemophiliacs

The relation between maternal religion and number of children is described in Table 3. Catholic mothers had larger families (including a greater number of children born after the birth of the first hemophiliac) than did Protestant mothers, but the significance of the difference (by Student's test) is greater for mothers born before 1930 than for mothers born in 1930 or later. The sample of Jewish mothers was small and their offspring few.

The effect of parity on the birth of further chil-

TABLE 2.—*Comparison of the Actual Number of Children Sired by Hemophiliacs and That Expected for Equal Numbers of Age-Matched Men of the General United States Male Population During Three Selected Five-Year Periods*

	HISTORICAL PERIOD								
	1940-1944 Number of Children			*1950-1954 Number of Children*			*1960-1964 Number of Children*		
Age of Men Years	*N**	*Actual*	*Expected*	*N**	*Actual*	*Expected*	*N**	*Actual*	*Expected*
15-19	55	0	1	86	0	2	195	1	4
20-24	40	4	4	68	1	11	169	9	32
25-29	22	2	3	54	1	11	86	9	20
30-34	23	2	3	42	4	6	65	4	10
35-39	7	1	1	22	2	2	56	2	5
40-40	1	0	0	23	0	0	42	2	2
Total, all ages	148	9	12	295	8	32	613	27	73
		not significant			$p = <0.01$			$p = <0.01$	

*N is the total number of patient-years under observation in each age and calendar-year group.

TABLE 3.—*Effect of Religion: Number of Children Born to Mothers of Hemophiliacs, as of 1971*

Year of mother's birth	*Number of mothers*	*Religion*	*Average total number of children*		*Average number of children born after first hemophiliac*	
Before 1930	107	Protestant	3.2	$p = <0.01$	1.3	$p = <0.1$
	52	Catholic	4.1		1.8	
	8	Jewish	1.9		0	
1930 or later	78	Protestant	2.5	$p = <0.1$	0.9	not significant
	39	Catholic	3.0		1.2	
	3	Jewish	1.3		0.3	

dren to women who had already had a hemophiliac son is described in Table 4. A tendency to limit further reproduction, relative to the pattern seen in the general population, was greater in women with only one or two children and less in women with three or four children.

We also wondered whether the relative position of the first hemophiliac son in the birth-order affected the number of further siblings born. The diagnosis of severe hemophilia may not be made until a child is several months old; at that time, a sibling may already have been conceived. The parents are more likely to know the diagnosis of hemophilia by the time they conceive a second sibling. We therefore compared the probability of third births to women who had borne a first hemophiliac child and a second normal child with the probability of third births to women who had borne a first normal child and a second hemophiliac child. No difference was found.

We also could find no difference in the number of further births after the birth of the first hemophiliac son to women who had no previous family history of hemophilia and to women who were known to be obligatory or potential carriers as primigravidas.

The effect of the historical period on births to carriers is described in Table 5. In the general United States population there was a low birthrate in the early 1940's, a rapidly rising rate after the Second World War, a peak in the late 1950's and a decline thereafter. The rate of births to carriers followed this general pattern, but the decline in the 1960's was more pronounced in carriers than in the general population. A significant difference between the actual number of births and expected number of births in carriers was demonstrated only for the period 1955-1968.

Discussion

In Southern California, most adults with hemophilia marry. The incidence of marriage may increase as the physical condition of patients continues to improve, and as their employment opportunities widen. The absolute number of married hemophiliacs is expected to increase sharply in the next decade as the large population of hemophiliacs born between 1945 and 1960 reaches the prime age for marriage. Despite the improved condition of hemophiliacs, and the belief expressed by many that a cure for hemophilia will be found by the time they become grandfathers, there has been no increase in the number of children sired by hemophiliacs over the past three decades. As the number of hemophiliac adults increases, however, we may expect an increase in the *absolute number* of obligatory carriers born.

We have not compiled information about the number of obligatory or potential carriers who have had no children, or who have had no hemophiliac son. Among women who have at least one hemophiliac son, further births appear to be influenced by some of the same factors, such as religion and historical period, which influence births in the general population. The birthrate in the United States is now falling, due perhaps to better and more easily available methods of contraception and abortion and to public approval of population control. In Southern California in the 1940's and early 1950's the number of births to

TABLE 4.—*Effect of Parity: Actual Births to Mothers of Hemophiliacs Compared with Expected Births to Women of the United States Population Matched for Exact Age (Range 20-39 Years) and Exact Calendar Year According to Parity*

Patient-years at risk		*Births*		*Significance of difference*
		Actual	*Expected*	
As para one: 582	Second child:	71	105	p=<0.01
As para two: 864	Third child	60	105	p=<0.01
As para three: 541	Fourth child	53	58	p=<0.5
As para four: 319	Fifth child	26	39	p=<0.05

TABLE 5.—*Effect of Historical Period: Comparison of Actual Births to Women Who Were Already Mothers of Hemophiliacs and Who Were Aged 20-39 Years and Were Para 1-4 to Births Expected of Equal Numbers of Women of Matched Age and Parity of the General Population*

Calendar Years	*Woman-years at Risk*	*Actual Births*	*Expected Births*	*Actual Births as Percent of Expected Births*	*Significance*
1940-44	158	17	19	90	not significant
1945-49	235	26	31	84	p=<0.5
1950-54	421	40	37	108	not significant
1955-59	461	54	74	73	p=<0.02
1960-64	575	48	77	62	p=<0.01
1965-68	528	25	44	57	p=<0.01

carriers was similar to that expected of women generally. Thereafter the birthrate among carriers decreased even more sharply than that of the general population. The threat of hemophilia plus a social climate favorable to small families may have a synergistic influence on carriers. The improved lot of the hemophiliac with modern treatment methods has not been associated with an increased birthrate among their mothers.

The desire for freedom from coercion in the decision for reproduction, as expressed by members of the London Haemophilia Society, is reasonable in a free society. However, a decision by some persons to have children may conflict with the desire of other members of society not to be additionally burdened. Those members of society who want to reduce the number of handicapped or dependent persons should not assume that genetic counseling alone will necessarily have the effect they seek. Genetic counseling, as practiced at present, is primarily informational: persons having a defective gene are identified and told the probability of having affected descendents. The counselor may communicate an attitude of approval or disapproval of reproduction, but the person being counseled is likely to be more strongly influenced by his own and his family's attitudes and desires.

Optimally, genetic counseling includes psychological counseling. The motivations for parenthood may be explored, and unrealistic hopes and exaggerated fears may be relieved. Alternative sources of fulfillment may be suggested for appropriate persons. For many people, however, there will be no reasonable substitute for the personal satisfactions of parenthood, and the general social forces encouraging reproduction may be strongly felt. For example, a young woman who is a potential carrier may still feel that the route to family and social approval is through marriage and childbearing: better to risk a hemophiliac son than to have no child at all. Parents who already have a hemophiliac son may want to have more children, hoping these will be normal and more likely to thrive and succeed. A hemophiliac, denied vigorous physical endeavors if not actually disabled and often frustrated in his attempts at a career, may seek to express his manliness and competence by fathering a generation of healthy children. To a disabled man, children may seem especially important as potential sources of emotional and material support.

Some people, therefore, who have had the benefit of optimal genetic and personal counseling, may decide that they do want to have children. We must continue to expect some perpetuation of hemophilia through reproduction by some persons who know they bear the defective gene.

REFERENCES

1. Discombe G: Personal view. Br Med J 1:723, Mar 27, 1971
2. Miller M: To be or not to be a parent? Evening News (London) Mar 26, 1971
3. Living reply to "baby ban" doctor. Sunday Mirror (London) Mar 28, 1971
4. Haemophilia Society replies on parenthood. The Times (London) Mar 27, 1971

Refer to: Shulman AG: High bulk diet for diverticular disease of the colon. West J Med 120:278-281, Apr 1974

In the past century diverticular disease of the colon has changed from being almost unknown to becoming the most common disease of the colon. Studies in Britain indicated that the pathological basis of the disease is a thickening of the colonic musculature, with diverticulosis and diverticulitis developing because of increased intracolonic pressures generated by the thickened colon wall. This pressure can be sharply reduced by increased colonic bulk. Geographical and anthropological data reveal that diverticular disease results from Western civilization's food habits, specifically the reduced fiber content in food. There is evidence that increasing the dietary intake of fiber by the addition of bran can prevent formation of diverticula and relieve the symptoms of established disease. Large scale studies are recommended both as treatment and to further test the validity of this concept.

High Bulk Diet for Diverticular Disease of the Colon

ALEX. G. SHULMAN, MD, *Los Angeles*

DURING THE PAST DECADE the treatment of diverticular disease of the colon has been vigorously discussed and debated in the British literature. The older concept of treating this condition by a low residue bland diet has been challenged by Burkitt,[1] Painter[2] and others. They offer evidence that diverticular disease, which affects one out of three people over age 40 and two out of three over age 80 is a result of the relatively low residue diet of Western civilization. They, therefore, conclude that such a diet can act only adversely on this condition.

From the Department of Surgery, Cedars-Sinai Medical Center, Los Angeles.

Submitted September 5, 1973.

Reprint requests to A. G. Shulman, MD, 8920 Wilshire Blvd., Beverly Hills, CA 90211.

Therapeutic investigations appropriate to the increasingly large numbers of people affected by the disease have not been forthcoming in the United States. It is the intent of this paper to clarify some of the newer concepts of colonic diverticular disease in order to try to stimulate such programs.

While nutrition experts generally agree that an adequate diet requires sufficient proteins, carbohydrates, fats, minerals, vitamins, water and trace elements, the specific need for "bulk" in the diet has been ignored. On the contrary, the "bland" or "soft" diet has been recommended traditionally for almost every gastrointestinal disorder. Evidence will be presented here to suggest the beneficial aspects of a high bulk diet and its salutary

effect on the symptoms caused by colonic diverticular disease.

Pathophysiology

The primary pathological state leading to diverticula has been shown to be excessive development of the circular and longitudinal muscle coats of the colonic wall. This causes increased intracolonic pressure which alone may cause most of the symptoms generally attributed to diverticular disease. It is only as a result of this muscle thickening that diverticula later develop.[3-5]

Small, hard stools cause excessive contraction of the colon in its attempt to expel them. Over a period of many years irregular thickening of circular muscle bands occurs and may ultimately cause temporary complete closure of the colonic lumen. This may account for the "cramps" which are often experienced. If adjacent areas of closure occur simultaneously, closed spaces develop between them and in these closed spaces enormous pressures can be created. It is this repeated build-up of pressure in the closed segments which has been shown to be responsible for the extrusion of mucosal pouches through weak points in the muscular wall to form diverticula.

In a study of surgical specimens of the colon removed for clinical evidence of "diverticulitis," Morson[6] noted that while thickening of the muscular walls was present in all cases as expected, in one third of them there was no evidence of inflammation.

Fleischner, in his pioneering work in this field[6a] defined the nature of "acute diverticulitis" as usually being a peridiverticulitis which results from an earlier perforation of a diverticulum and subsequent extrusion of bowel contents. He thereby refuted the earlier notion that diverticulitis was due to an abscess within a diverticulum, similar to the pathological state seen in acute appendicitis. He further speculated that the high intracolonic pressure found in diverticular disease may be the initial cause of the perforation.

Animal Studies

When rats are fed on a low residue diet, colonic diverticula develop in a significant number.[7] Rabbits that were on an ad lib diet of white bread, butter, milk, sugar and vitamins—that is, a soft diet—for four months, gained weight, became constipated, had a five-fold increase in intracolonic pressure and acquired colonic diverticula.[8]

Defunctionalized Bowel

Since areas of acute diverticulitis usually improve when the colon is defunctionalized, one would not expect diverticulitis to develop *de novo* in a colon long defunctionalized. Yet McCarthy and Picazo reported acute sigmoid diverticulitis with fistulization in a colon segment which had not been functioning for 30 years.[9] Hughes,[10] examining autopsy material consisting of diverticular colons, found that the most pronounced bowel wall thickening was in a defunctionalized limb. Roentgenologists have long observed this intense state of contractility in defunctionalized colonic limbs. If the empty colon remains more or less contracted, the almost empty colon resulting from years of a low residue diet would also be expected to be in a frequently contracted state.

Geographical Data

According to repeated statistics from Africa, diverticulosis coli is virtually unknown among rural natives even when extensive roentgen studies are made to find it.[11-13] It is almost unknown also in underdeveloped areas in India, Korea, Indonesia and elsewhere. Common to the peoples of those places is the custom of eating unrefined whole grain as a staple of diet. As native Africans settle in Western countries and adopt their food patterns (as have American blacks) the incidence of colonic diverticula among them becomes the same as in the whites.[14]

Bowel Transit Time

For rural African natives, bowel transit time averages about 35 hours. This contrasts sharply with a time of 75 to 100 hours for the average Englishman. With the shorter transit time the stools are moist and bulky, and are evacuated without effort about twice daily. The slower-passing stools of persons who dwell in more urban settings tend to be small, dry, hard and constipating, and greater intracolonic pressure is needed to propel them along the bowel.

Implications of Modern Milling Methods

Following the introduction of the roller-milling of flour in the western world about 1880, almost all of the bran fiber was removed from wheat, making the flour, which was a staple of diet, less bulky. Within 40 years or so of the widespread use of bread made of this flour, diverticular dis-

ease, which had been a pathological rarity in the late nineteenth century, had become common. It is estimated that today 40 million Americans have it.

In 1860, the fiber content of white flour was 0.2 to 0.5 percent and the average amount consumed daily in bread was between 1.1 and 2.8 grams.[15] By 1967, bread consumption having been gradually reduced to half the 1860 level and total fiber content to between 0.01 and 0.04 percent, the average daily intake of wheat fiber was 0.1 gram or less.[16] Modern man, then, eats about one-tenth to one-twentieth the amount of cereal fiber that was contained in the ordinary diet a century ago. Painter and Burkitt[1] expressed belief the increased incidence of diverticular disease in our society may be due to this reduction. They recommend that whole grain bread be substituted for white in the diet, and suggested that small amounts of cereal fiber be added to the daily intake to make up for the nutritional deficiency.

Treatment of Diverticulosis and Diverticulitis

Even though a number of American gastroenterologists have expressed grave doubts of the value of the bland, low-residue diet for diverticular disease, most have remained reluctant to change to a trial of the high residue diet. Painter, Almeida and Colbourne[17] challenged this reticence by treating symptomatic diverticular disease with a high residue diet that included unprocessed bran. Their recommended diet includes fresh fruit, vegetables, and whole meal bread. However, for many elderly British pensioners such a diet can be prohibitively expensive. As an effective alternative, they have advised the simple addition of a small amount of bran daily to the patient's usual diet. Bran, absorbing water from the colonic wall, produces the desired bulk and in this role is much more effective than are fruits and vegetables.

Seventy patients with symptomatic diverticular disease were so treated. To make it more palatable, unprocessed bran was added to cereals, soups, milk or fruit juice. In its pure state, unprocessed bran looks and tastes like brown sawdust. Beginning with two teaspoonfuls three time a day (6 grams a day) for two weeks the amount was increased gradually to the level at which soft stools were passed easily once or twice daily. At first the patients reported flatulence and a feeling of distension but they were instructed to continue the diet, as these symptoms would disappear in three to eight weeks. Of 62 patients who stayed on the diet for an average of 22 months, 88 percent expressed significant relief of their pretreatment symptoms of pain, distension, colic, nausea or constipation. On follow-up four years later, all were improved. Painter suggested that "roughage" is an unfortunate term and that bran, when moistened, clearly becomes "softage."

Hydrophillic colloids, such as methylcellulose, in tablet form, were reported by Hodgson[17] to have brought similar results in a small group of patients, but Almeida warned that bowel obstruction may be caused by such treatment.[18]

Discussion

Diverticulosis alone, with no evidence of inflammation, can cause colonic pains and other symptoms: Nicholas and coworkers[19] reported only diverticulosis in 14 percent of colon specimens surgically excised for diverticulitis—these cases thus fitting Painter's category of "painful diverticular disease."

When it was originally proposed in the 1920's, the low residue diet for diverticular disease was based on the assumption that hard food particles cause inflammation—a notion that went unchallenged for 40 years though it did not help the condition and the serious complications steadily continued.

Much impressive geographical and statistical evidence is accumulating to suggest that the low residue diet of Western civilization, much of it preprocessed and precooked, is the main factor in the increasing incidence of diverticular disease as well as a number of other common disease states.[20] The epidemic increase of diverticular disease alone should warrant a long-term controlled trial to learn if diverticula can be prevented. Several leading authorities in this country[21-23] have suggested that a high bulk-producing diet for symptomatic patients, or the addition of bran to their regular diet, should be tried. Yet the term "soft diet" seems to conjure such benefits that apparently there is a reluctance to deviate from it.

So credible and impressive was the large amount of evidence presented by Burkitt in a hospital lecture series given recently in Los Angeles that many of the originally skeptical physicians who made up the audience became reasonably convinced of its merit. It was even more revealing that a significant number of these physicians were soon eating bran regularly.

Today there exists in the American literature a wide variety of recommendations for the man-

agement of asymptomatic diverticular disease. They range from advocacy of a bland diet with nuts, seeds and fibrous foods strictly prohibited,[24-26] to the other extreme of a high residue diet.[27,28] In between are those who advise no dietary restriction but the addition of bulk-forming psyllium seed hydrophillic colloids (Metamucil®). Spiro[29] said that advice to avoid seeds and nuts "has antiquity alone to recommend it."

A recent study of symptomatic patients who were instructed to refrain from eating high-residue foods is informative. Those patients who followed their doctors' orders continued to have symptoms, whereas those who did not were symptom-free.[30]

It must be added that there are a few people who cannot tolerate bran or high bulk-producing foods. Others, a rare few, may have a genetic sensitivity to glutens which precludes their eating wheat, oats, rye or barley.

REFERENCES

1. Painter NS, Burkitt DP: Diverticular disease of the colon: A deficiency disease of Western civilization. Br Med J 2:450-454, 1971

2. Painter NS: Diverticular disease of the colon—A disease of Western civilization. D M Jun, 1970

3. Painter NS: The aetiology of diverticulosis of the colon with special reference to the action of certain drugs on the behavior of the colon. Ann R Coll Surg Engl 34:98-119, 1964

4. Arfwiddson S: Pathogenesis of multiple diverticula of the sigmoid colon in diverticular disease. Acta Chir Scand (Suppl) 342:1-68, 1964

5. Parks TG: Reappraisal of clinical features of diverticular disease of the colon. Br Med J 4:642-645, 1969

6. Morson BC: The muscle abnormality in diverticular disease of the sigmoid colon. Br J Radiol 36:385-392, 1963

6a. Fleischner FG: Diverticular disease of the colon. Gastroenterology 60:316-324, 1971

7. Carlson AJ, Hoelzel F: Relation of diet of diverticulosis of colon in rats. Gastroenterology 12:108-115, 1949

8. Hodgson J: An animal model to study diverticular disease. Brit J Surg 59:315, 1972

9. McCarthy JD, Picazo JG: Diverticulitis—A case reflecting upon pathogenesis. Diseases of colon and rectum 12:451-452, 1969

10. Hughes LE: A study of abnormal muscular patterns in diverticular disease of the colon using polysiloxane foam enema. Gut 11:111-117, 1970

11. Keeley KJ: Medical proceedings 4:281, 1958

12. Trowell HC: Non-infective Diseases in Africa. London, Arnold, 1960

13. Cleave TL, Campbell GD, Painter NS: Diabetes, Coronary Thrombosis and the Saccharine Disease, 2nd Ed. Bristol, Wright, 1969

14. Robertson J: Changes in the fiber content of the British diet. Nature 238:290-292, 1972

15. Kent-Jones DW, Amos AJ: Modern Cereal Chemistry, 6th edition, London Food Trade Press 185-189, 1967

16. Painter NS, Almeida AZ, Colebourne KW: Unprocessed bran in treatment of diverticular disease of the colon. Br Med J 2:137-140, 1972

17. Hodgson J: Effect of methylcellulose on rectal and colonic pressures in the treatment of diverticular disease. Br Med J 3: 729-731, 1972

18. Almeida AZ: Methylcellulose in diverticular disease (Letter to the Editor). Br Med J 4:792, 1972

19. Nicholas GG, Miller WT, Fitts WT et al: Diagnosis of diverticulitis of the colon. Ann Surg 176:205-209, 1972

20. Burkitt DP: Epidemiology of cancer of the colon and rectum. Cancer 28:3-13, 1971

21. Berman PM, Kirsner JB: Diverticular disease of the colon in the elderly. Geriatrics 27:70-75, 1972

22. Stahl WM: Answer to letter to editor. JAMA 221:1058, 1972

23. Almy TP: Answer to letter to editor. JAMA 221:1058, 1972

24. Paulson M: Gastroenterologic Medicine. Philadelphia, Lea and Febiger, 1969, p 1518

25. Bockus HL: Gastroenterology, Vol 2. Philadelphia, W B Saunders, 1964, p 931

26. Harrison TR: Principles of Internal Medicine, 6th Ed, McGraw-Hill, 1970, p 1504

27. Krupp MA, Chatton MJ: Current Diagnosis and Treatment. Los Altos, Lange Medical Publications, 1972, p 340

28. Beeson BP, McDermott W: *In* Cecil-Loeb Textbook of Medicine, 13th Ed. Philadelphia, W B Saunders Co, 1971, p 1258

29. Spiro HM: Clinical Gastroenterology. Collier-MacMillan Ltd. London 1970, p 555

30. Eusebio EB, Eisenberg MM: Natural history of diverticular disease of the colon in young patients. Am J Surg 125:308-311, 1973

Refer to: Hawkins DB, Seltzer DC, Barnett TE, et al: Endotracheal tube perforation of the hypopharynx. West J Med 120:282-286, Apr 1974

Endotracheal Tube Perforation of the Hypopharynx

DONALD B. HAWKINS, MD, DAVID C. SELTZER, MD, THOMAS E. BARNETT, MD, *and* GEORGE B. STONEMAN, MD, *Los Angeles*

Perforation of the hypopharynx or esophagus is a serious though not often reported complication of endotracheal intubation. Only 12 cases had been reported before the eight which are presented here to emphasize this hazard of intubation. The early symptoms of perforation, which occurred during insertion of the tube, were: subcutaneous emphysema (seven patients), mediastinal emphysema (six), pneumothorax (two), cardiac arrest (one). One patient had no recognized early signs of perforation, but presented with an abscess of the mediastinum six weeks later. The site of perforation, determined by endoscopy in six patients, was the lateral hypopharynx in four, and the vallecula in two. The outcome of the eight perforations was as follows: two patients recovered on conservative management; in two, abscesses of the neck and in one an abscess of the mediastinum developed. All three recovered after drainage of the abscesses. Three patients died. Two outstanding characteristics of these eight cases were that in all of them intubation was attempted by physicians relatively inexperienced in the technique, and in all but one it was done in emergency. Since the use of intubation in emergency situations is increasing, all physicians in training should receive formal instruction in technique.

ALMOST A CENTURY has passed since MacEwen[1] published his "Clinical Observations on Introduction of Tracheal Tubes by the Mouth." His use of intubation in three patients in 1878 demonstrated the value of this approach. Endotracheal intubation is now widely accepted as an effective technique for administering anesthesia and for providing an airway in emergency. Most reports of complications deal with those resulting from prolonged intubation, or pressure from the tube or its cuff. Trauma from the act of inserting the tube has received less attention.

When traumatic intubation is discussed, it is usually in relation to trauma of the larynx.[2] Perforation of the hypopharynx or esophagus is often mentioned as a possibility[3] but is seldom

From the Department of Otolaryngology, University of Southern California School of Medicine, Los Angeles.

Presented at the meeting of the Pacific Coast Oto-Ophthalmological Society, Portland, Oregon, May 10, 1973.

Submitted September 11, 1973.

Reprint requests to: D. B. Hawkins, MD, Los Angeles County/USC Medical Center, Box 296, 1200 North State Street, Los Angeles, CA 90033.

reported. In the past three years at the Los Angeles County/University of Southern California Medical Center eight patients in whom the hypopharynx had been perforated during insertion of endotracheal tubes were referred to the Department of Otolaryngology for consultation.

Seven of the eight patients were adults, one an infant two days old. Five were female.

The conditions which necessitated intubation were as follows: Four of the patients had taken an overdose of drugs, one had a cerebral-vascular accident, one had cardiac arrest, and the two-day-old infant, who was premature, had respiratory distress syndrome. One was undergoing routine intubation for surgical anesthesia.

Definitive intubation was by the oral route in five patients, the nasal route in three. In two of the patients with nasal intubation, attempts by the oral route had failed. Stylets were used in all oral attempts except in the newborn infant.

Intubation was performed, or attempted, by physicians in several different specialties. Three were performed by emergency room physicians, two by members of the medical staff, and one each by pediatric, obstetrical, and oral surgery house staff. Three patients were intubated by anesthesiologists after unsuccessful attempts by other physicians.

The signs that indicated a perforation had occurred were as follows: Subcutaneous emphysema of the neck was noted in seven patients. Mediastinal emphysema was demonstrated by chest film in six of these seven. Pneumothorax developed in two of these six. In one, a rapidly developing tension pneumothorax precipitated cardiac arrest. One patient had no recognized immediate signs of perforation, but presented six weeks later with an abscess of the mediastinum.

All patients from whom a history could be obtained complained of throat pain, especially on swallowing. Fever was not a significant early symptom.

The site of perforation was determined by endoscopy in six patients. Diagnostic endoscopy was deferred in two because of their critical condition. In four patients, perforations were found in the lateral wall of the hypopharynx. In two, the site of injury was the vallecula.

Both patients in whom endoscopy was deferred died. Autopsy was performed on only one. This was done by the coronor's office; the hypopharynx was not mentioned in the autopsy report. There can be little doubt that perforations occurred in these two patients. In both, there was a history of difficult oral intubation in emergency, followed shortly by subcutaneous and mediastinal emphysema, and in one case by pneumothorax.

Two of the eight patients recovered on conservative management without complications. They had perforation of the vallecula and lateral wall of the hypopharynx respectively. In the other patient with perforation of the vallecula, and one with perforation of the lateral wall, abscesses of the neck developed. In a patient with perforation of the lateral hypopharyngeal wall an abscess developed in the mediastinum. All three recovered after drainage of the abscesses. Three patients died, two adults and the newborn infant. The infant might have died of his underlying disease, but pneumothorax developed secondary to the lateral hypopharyngeal perforation, and this played a significant role in his death. The adult who was intubated for cardiac arrest died of the underlying condition. The perforation was not a factor in his death. In the other adult, who had taken an overdose of a drug, death was directly attributable to the perforation. She did not recover from cardiac arrest secondary to tension pneumothorax that was due to the perforation.

Reports of Two Cases

Case 1. A 43-year-old woman was admitted because of an overdose of barbiturates. She had first been taken to an outside emergency room. A physician there had attempted unsuccessfully to pass an endotracheal tube. She arrived at the Los Angeles County/University of Southern California Medical Center, comatose, with an oral airway in place. An anesthesiology resident introduced an endotracheal tube without difficulty. On examination at that time subcutaneous emphysema of the neck spreading to the chest was noted. An x-ray film showed mediastinal emphysema. An otolaryngology consultation was obtained. On direct laryngoscopy a perforation of the right vallecula was seen. Tracheostomy was performed.

As the patient was allergic to penicillin, sodium cephalothin (Keflin®) was given by vein. She had a febrile course for five days, mainly from right lower lobe pneumonia. Eleven days after admission, she was asymptomatic. Indirect laryngoscopy revealed apparent healing of the vallecular injury. The tracheostomy was closed. She was discharged on the fifteenth hospital day, antibiotics having been discontinued. Six days later, she returned with a tender, fluctuant swelling in

Figure 1.—(Case 1) **Left,** lateral x-ray film of the neck showing widened prevertebral space, with an air-fluid level opposite the third and fourth cervical vertebrae. **Right,** barium swallow showing deflection of the hypopharynx and esophagus by the mass to the left. The air-fluid level is shown in the left side of the neck.

the left side of the neck. An inward bulging of the left pharyngeal wall was seen laryngoscopically. A lateral x-ray film of the neck (Figure 1) demonstrated a widened prevertebral space with an air-fluid level opposite the third and fourth cervical vertebrae. Barium swallow (Figure 1) showed the hypopharynx and esophagus to be deflected to the right by the mass. The air-fluid level was shown to be in the left side of the neck. Administration of Keflin was begun again. The abscess was drained through an external incision. The patient did well and was discharged a week later. There was no recurrence of the abscess.

Case 2. The patient, a 49-year-old woman, had had excision of the uvula for squamous cell carcinoma in May 1969. Left radical neck dissection for a metastatic node was performed in September 1970. There had been no evidence of further recurrence.

On 10 October 1971, after a bout of heavy drinking, she took several gluthemide (Doriden®) tablets and soon became unconscious. She was taken to the emergency room of another Los Angeles hospital and a physician there inserted an endotracheal tube, which was removed after a short time when she became responsive. She was transferred to the medical service of the Los Angeles County/University of Southern California Medical Center for overnight observation.

On 29 November 1971 she was admitted to the otolaryngology service with a history of sore throat and retrosternal pain since the episode six weeks earlier. A progressive swelling had developed in the left side of the neck. Two days before admission this began to drain through a small opening in the surgical scar low in the left side of the neck. By Valsalva maneuver the patient could express pus from this fistulous opening, and water taken by mouth passed through it.

A lateral x-ray film showed a widened prevertebral space with an abscess cavity at the level of the seventh cervical vertebra (Figure 2). A contrast esophagram demonstrated partial filling of this abscess cavity in the superior mediastinum.

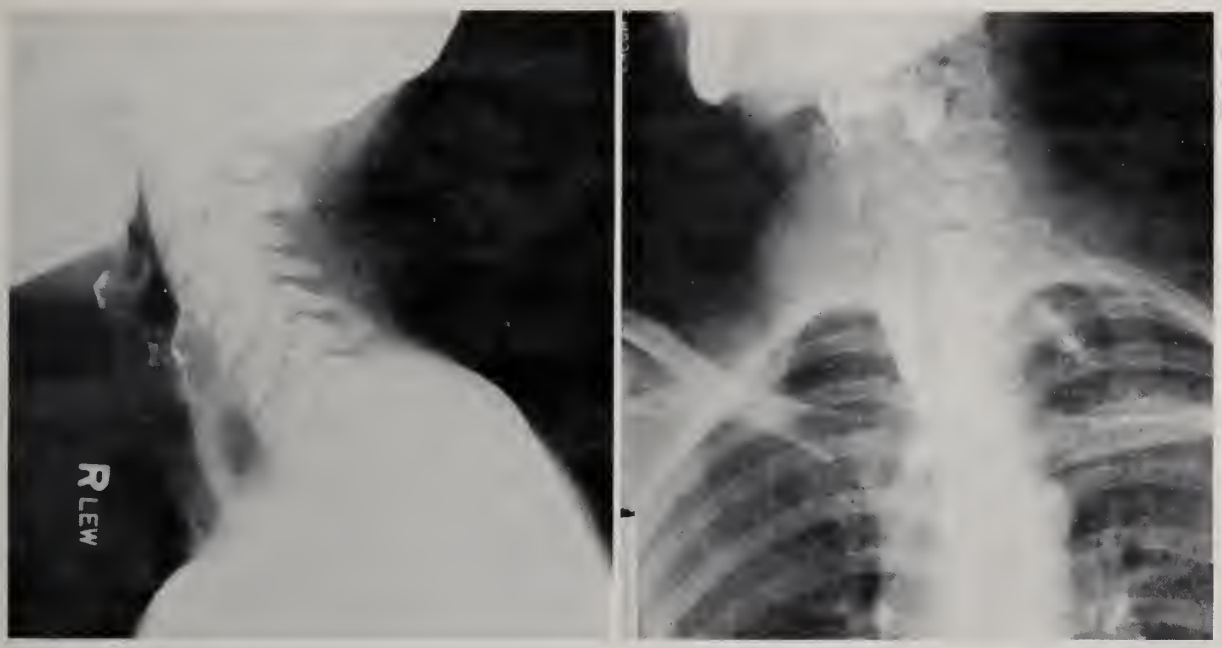


Figure 2.—(Case 2) **Left,** lateral x-ray film of the neck showing widened prevertebral space with an abscess cavity at the level of the seventh cervical vertebra. **Right,** contrast (Hypaque®) esophagram demonstrating the abscess cavity in the superior mediastinum.

The cavity was posterior and to the left of the esophagus, and extended 12 cm inferiorly (Figure 2).

On esophagoscopic examination a pinpoint opening was seen in the left side of the hypopharynx just above the cricopharyngeus. Pus was obtained from this opening by suction. There was no evidence of recurrent carcinoma.

In conjunction with the thoracic surgery service, the patient was managed non-surgically with nothing by mouth, nasogastric tube feedings, and high doses of penicillin intravenously. The neck fistula closed in nine days. A contrast esophagram 12 days after admission showed no abnormality. The patient was discharged six days later.

She returned after a week with recurrence of purulent drainage from the left side of the neck. An esophagram showed no fistulous connection with the hypopharynx this time. Methicillin was given intravenously. The abscess was drained by a cervical approach, the fistulous opening in the neck was excised, and the fistula tract was probed medially and inferiorly for a distance of 9 cm. A rubber catheter was inserted and attached to low suction. By the fourth postoperative day, drainage from the catheter was minimal. Hypaque® instilled through the catheter on the seventh day showed no residual abscess cavity. A barium esophagram was normal. The catheter was advanced slowly, then removed on the 12th day.

The patient was discharged on the 15th postoperative day. There was no recurrence of the abscess.

Discussion

Five of the eight cases of perforation of the hypopharynx reported herein occurred in a period of three years at the Los Angeles County/University of Southern California Medical Center where more than twelve thousand intubations, surgical and emergency, are performed yearly. Three were referred from a wide area of Los Angeles. It seems probable, however, that it occurs more often than is indicated by the literature. We could find only 12 reported cases of perforation of the hypopharynx from endotracheal tubes,[10-18] as distinct from lacerations of the nasopharynx from passage of nasotracheal tubes.[4-9]

Perforation of the hypopharynx should be suspected if subcutaneous emphysema is noted after intubation, especially if introduction of the tube was difficult. If perforation is suspected, the patient should be given nothing by mouth, and antibiotics should be started. Posterior-anterior and lateral x-ray studies of the neck and chest should be obtained. An esophagram using non-irritating contrast material such as Hypaque® may demonstrate the perforation. In only one of our patients, however, was the diagnosis made by Hypaque swallow before endoscopy. This was the patient

presenting with a mediastinal abscess six weeks after intubation.

Two outstanding characteristics were evident in the series of eight cases here reported:

1. In all but one, intubation was done in emergency outside the operating room.

2. In all cases the procedure was performed, or attempted, by physicians who may have had little formal training in the technique.

Serious complications rarely occur when intubation is carried out by well trained personnel under controlled conditions in the operating room. In uncontrolled emergency situations, trauma is more likely to occur, for time is a critical factor and exposure of the larynx may be difficult. Under these conditions, there is a tendency, especially among physicians with little intubation experience, to hyperextend the neck, insert the laryngoscope to the base of the tongue, and probe with the endotracheal tube.

Hyperextension of the neck accentuates the anterior position of the larynx in relation to the pharynx. The base of the tongue and the epiglottis are displaced posteriorly. These structures are more difficult to elevate in this position; intubation is more difficult, and trauma is more likely. The proper position for exposure of the larynx is slight flexion of the neck on the chest, and extension of the head on the neck. This is also the best position for intubation. In emergencies, this position can be obtained by placing a roll, or a small pillow, beneath the patient's neck but not beneath the shoulders. The head should be elevated; the shoulders should be flat.

The use of intubation in emergency situations will probably increase in coming years. Since any physician in any specialty may find himself needing to know how to do it, all physicians, in medical school and again in their residency, should receive training in the technique. Emphasis should be placed on anatomy of the larynx and pharynx, proper head positioning, and exposure of the larynx before inserting the tube.

Eight patients are reported who sustained perforations of the hypopharynx during insertion of endotracheal tubes. Three of these died; the perforation was a significant factor in the death of two.

Endotracheal tube perforation of the hypopharynx is a serious complication. It is more of a hazard in emergency situations. Perforations should be suspected if subcutaneous emphysema is noted in the neck after intubation, especially if the intubation was difficult.

REFERENCES

1. MacEwen W: Clinical observations on the introduction of tracheal tubes by the mouth instead of performing tracheotomy or laryngotomy. Br Med J 2:122-124, 163-165, 1880
2. Smith OS, Hemenway WG, English GM, et al: Post-intubation subgottic granulation tissue: review of the problem and evaluation of radiotherapy. Laryngoscope 79:1227-1251, 1969
3. McGovern FH, Fitz-Hugh GS, Edgemon LJ: The hazards of endotracheal intubation. Ann Otol 80:556-564, 1971
4. Barnard J: An unusual accident during intubation. Anesthesia 3:126-129, 1948
5. Coffin S: Tears of the pharyngeal mucous membrane during intubation. Anesthesia 5:104-108, 1950
6. Brown WM: Blind intubation. Anesthesia 7:118-123, 1952
7. Gaisford JC, Hanna DC, Monheim L: Endotracheal anesthesia complications associated with head and neck surgery. Plast Reconst Surg 24:463-471, 1959
8. Seltzer AP: Complications of nasotracheal intubation. J Nat Med Assn 61:415-422, 1969
9. Manheim A, Perez RE, Nevin JE: A rare complication from a not-so-rare occurrence (endotracheal intubation). South Med J 64:814-819, 1971
10. Adelman MH: Perforation of the pyriform sinus: A sequela of endotracheal intubation. J Mt Sinai Hosp 19:665-667, 1952-53
11. Smith RH, Pool LL, Volpitto PP: Subcutaneous emphysema as a complication of endotracheal intubation. Anesthesiology 20: 714-716, 1959
12. Doig VF: Perforated esophagus, an acute emergency. Am J Surg 26:361-366, 1960
13. Bryant FL: Discussion. Trans Amer Bronchoesoph Assn, 1963, p 122
14. Leigh TF, Achord JL: Pharyngeal and esophageal perforations during instrumentation. Am J Roentgen 91:757-765, 1964
15. Grover LK: Instrumental perforation of the esophagus: What is conservative management? J Thorac Cardiovasc Surg 52: 1-10, 1966
16. Wychulis AR, Fontana RS, Payne WS: Instrumental perforations of the esophagus. Dis Chest 55:184-189, 1969
17. Wolff AP, Kuhn FA, Ogura JH: Pharyngo-esophageal perforations associated with rapid oral endotracheal intubation. Ann Otol 81:258-261, 1972
18. Berry BE, Ochsner JL: Perforation of the esophagus. J Thorac Cardiovasc Surg 65:1-7, 1973

Refer to: Specht EE: Coxa plana (Legg-Perthes disease) (Medical Progress). West J Med 120:287-294, Apr 1974

Medical PROGRESS

Coxa Plana (Legg-Perthes Disease)

ELMER E. SPECHT, MD, *San Francisco*

Legg, Calvé and Perthes are associated with the identification of coxa plana as a distinct pathological entity of the hip in childhood because of their papers published in 1910.[1-3] However, Axhausen in 1909[4] had already recognized "poor circulation" of the femoral head as a possible cause of juvenile arthritis deformans coxae. One can also find other earlier reports of such cases.[5,6] But it was not until the decade following Roentgen's description of "a new kind of ray" that this condition was clearly distinguished from other hip afflictions of childhood, chiefly tuberculous coxitis, which was then common and was often treated by excision of the joint. In fact, Waldenström[7] described coxa plana quite well in 1909 but felt it was of tuberculous origin. Since 1910 coxa plana, aseptic necrosis of the hip, pseudocoxalgia or osteochondritis deformans juvenilis, as it has been variously known, has stimulated considerable interest because its cause and treatment remain uncertain.

Incidence

The incidence of this condition has been estimated at 0.44 per 1,000 children between ages three and fourteen years[8] in Denmark. It is estimated that one in 750 boys and one in 4,000 girls in the United States[9] are affected.

From the Department of Orthopaedic Surgery, University of California, San Francisco, School of Medicine.

Reprint requests to: E. E. Specht, MD, Department of Orthopaedic Surgery, University of California, San Francisco, San Francisco, CA 94143.

Cause of Legg-Perthes Disease

Although there has been general agreement, at least in recent years, that the essential pathological condition is ischemic or avascular necrosis,[10-18] the initiating cause of the vascular insult continues to be elusive. Trauma,[19,20] synovial effusion,[21-24] infection, vascular occlusion,[25,26] constitutional predisposition,[27] and genetic factors[8,27-35] have all been implicated but no unifying concept has been found that satisfactorily explains all the epidemiologic data. It seems likely that avascular necrosis of the femoral head may be the final common pathway of a number of initiating disorders, all of which disrupt a tenuous vascular supply to a tissue which responds rather dramatically to ischemia and, because of its laggard healing mechanisms, is very slow to reconstitute. Trueta and his associates[13] have clearly shown in injected autopsy specimens that the lateral epiphyseal, or retinacular, vessels of the posterior hip capsule are the sole supply of the femoral head, at least in caucasians between the ages of four and ten. This period of middle childhood is the period of high risk for Legg-Perthes disease, according to virtually all reports.

The regularly reported predominance of boys in nearly all series[27,36-41] by a ratio of about four to one and a similar predominance of males in fracture series in children[13,20] suggest trauma as being at least an occasional cause of the vascular insult. No differences in vascular supply in males

compared with females were found in a study by Trueta.[42] Trauma does not satisfactorily explain the 12 to 20 percent incidence of bilateral occurrence, however.

Familial instances have been reported[8,27,29] and there have been seven reports of concordant occurrence in both of monozygotic twins.[28,30,32,33,35] However, concordance is certainly not the rule and this indicates that any genetic predisposition must be that alone and not the fundamental cause of the avascularity. Here again it is tempting to postulate a genetically tenuous vascular supply acted upon by an environmental insult, such as subclinical trauma or transient synovitis, to explain the pathogenesis in these familial groupings.

Transient synovitis of the hip[21-23] has been reported as an antecedent of the condition in as many as 18 percent of patients with Legg-Perthes disease.[24] The mechanism of this is thought by some observers to be vascular tamponade of the posterior capsular vessels by increased hydrostatic pressure. Others[43,44] are unconvinced that transient synovitis leads to avascular changes. It seems likely that synovitis can do so, but uncommonly; probably it does not account for the majority of cases.

Race is clearly a factor, as is shown by the low incidence of the condition among black children. Trueta feels this is due to a different vascular pattern of the hip than that in whites.[13] The finding of apparent avascular necrosis in a black child makes it mandatory to obtain hemoglobin electrophoresis to rule out hemoglobinopathy.

Constitutional predisposition manifested by short stature[27,37,45] and delayed skeletal maturation[27,46,47] have been described in association with Legg-Perthes disease in some series, but the significance of this association is not clear. Hormonal influences have been inferred in humans and suggested in certain species of dogs, but extrapolation from one species to another is always hazardous. One human study[47] failed to find any hormonal alterations, although low birth weight in female patients was suggested. Other investigators have also found low birth weight to be significantly more common in coxa plana. Genitourinary anomalies and spina bifida occulta[48,49] have been reported as occurring more frequently in association with coxa plana, but these findings will require confirmation by other observers. Also, increased anteversion of the proximal femur in Legg-Perthes disease has been described,[50] but there is no general agreement on this point.[51]

Clinical Features and Prognosis

The characteristic appearance of the condition is well known: a four- to eight-year-old boy with a limp, usually of insidious onset, and frequently with minimal pain centered in the medial thigh and knee. In fact these characteristics were clearly described by Legg in his 1910 paper, "An Obscure Affection of the Hip-Joint."[2] In approximately 6 percent of patients, however, the condition begins in the acute phase and may be misdiagnosed as transient synovitis.[22] Pain may be aggravated by activity and diminished by rest. After the initial painful phase, which may last weeks or months, the acute symptoms subside and may be followed by gait alterations due to faulty biomechanics of the joint. An abductor (Trendelenburg, gluteus medius) gait, atrophy of the thigh, impaired hip abduction and internal rotation, and occasionally a flexion contracture of the hip may be found. Some cases are diagnosed only in retrospect by the finding on roentgenograms of characteristic changes in the femoral head and neck. There are no laboratory tests that are reliable in identifying the condition. Appropriate studies to rule out infectious arthritis, tuberculosis, hemoglobinopathy, hypothyroidism, Gaucher's disease, and multiple epiphyseal dysplasia may be indicated in certain patients; otherwise laboratory studies are not helpful. In instances of bilateral involvement, x-ray studies of other epiphyses should always be made in order to rule out generalized skeletal dysplasia. Osteoid osteoma and pigmented villonodular synovitis have also been confused with Legg-Perthes disease. The typical child with Legg-Perthes disease, then, is a white boy, four to eight years old, who has been in good health. Involvement is usually unilateral at first but may eventually become bilateral in 10 to 20 percent of patients.[22,52]

With regard to prognosis, there is general agreement that the younger the patient is at the onset of the condition, the better the outcome will be. This indicates that a long remaining period of growth may allow optimal remodeling of the joint surfaces. The incongruence of the joints which results in premature degenerative joint disease is thereby minimized. In point of fact, the long-term functional prognosis is often surprisingly good in spite of apparently discouraging roentgenographic studies and the initial clinical picture. One recent study[53] with a 30-year minimum follow-up showed an average of 91 points on a scale of 100 when clinical function was rated on the Iowa Hip Rat-

ing Scale. Another recent long-term follow-up study[54] showed that only three of eighty-eight patients had required surgical therapy, and only seven of the remainder expressed any interest in remedial operation. The majority had no limp or pain and had normal motion in the involved hip. Another long-term study[55] showed that 28 of 34 patients had no pain in the hips, with at most slight limitation of motion, an average of 33 years after onset. Still another series[56] showed similarly good clinical results ("fully active and free from pain") in 29 of 34 patients after 30 years.

That the long-term prospects for recovery are good is also supported by a recent study in which an attempt was made to diagnose retrospectively, from roentgenograms, the cause of degenerative joint disease in adults. In this study slipped capital femoral epiphysis and congenital dislocation of the hip appeared to be much more common as causes than did coxa plana. Even when the long-term outcome of the condition is judged from roentgenograms rather than clinically, the majority of studies report better than 50 percent good or excellent results,[37,57] especially when the onset was before age seven.[58] Recurrence of Legg-Perthes disease has been reported[59] but must be exceedingly rare.

Changes Shown on Roentgenograms

Most descriptions of Legg-Perthes disease have divided the progress of the pathological changes into four stages based on the roentgenographic findings.[11,61] These changes begin with the initial, or acute synovial, stage and proceed through the fragmentation, the reparative, and finally the residual, or definitive, stages.[39,62-64]

The initial roentgenographs may show only soft-tissue changes such as increased width of the joint space, attributed to synovial effusion, and an increase in the size of the shadow cast by the capsule. There may or may not be smallness of the ossification center on the affected side;[20] this sign may be seen best on a "frog-leg" lateral view, which should always be taken. Segmental infraction with or without collapse of the involved portion of the femoral head then follows within a few weeks or months. If only the anterior part of the epiphysis is involved, and no collapse occurs, the prognosis is relatively good.[57] As the head is subjected to loading stresses it undergoes impaction and becomes flatter and broader, and more radiodense in x-ray studies. This has been attributed to increased biological plasticity due to loss of blood supply.[15] The sclerotic appearance on roentgenograms resembles the "dead head" of avascular necrosis in the adult hip.

Radioisotope studies of patients with Legg-Perthes disease are being made at present. Preliminary data suggest that a pattern of decreased vascularity may obtain, unlike that seen in adult avascular necrosis. Following this, increased uptake of surrounding tissues suggests reactive hyperemia, and these sequential changes may be of significance in determining treatment and prognosis. Metaphyseal changes, subjacent to the plate, are always radiolucent in contrast to the sclerosis seen in the ossific nucleus, and suggest hyperemic osteolysis. These changes are followed by "fragmentation" of the head, further compression and thinning of the ossific nucleus, and broadening of the shadow of the neck. Why this broadening occurs is not apparent, though it may be part of the reparative process.

At this point, the "avascular," or fragmentation, stage, which lasts an average of 10.8 months, begins to merge imperceptibly into the regenerative or reparative stage, which on the average lasts 32 months.[39] There is progressive resorption of dense areas in such a manner that a somewhat moth-eaten look supervenes. The less dense areas seem to be new bone formation occurring by "creeping substitution." Most observers believe that, in spite of an apparently worse condition when judged by roentgenographic studies, the actual compressive strength of the head improves at this stage.

The residual, or definitive, stage of this succession occurs when the femoral head has been fully replaced by viable trabecular bone which shows a normal pattern in roentgenographs, but with greater or lesser degrees of deformity in the shape of the head. The usual configuration of the head is flattened, rather than spherical, thus the name coxa plana. This is accompanied by broadening and some shortening of the neck. The epiphyseal line often lies more horizontally than when normal and may fuse prematurely.[39] Secondary adaptive changes occur in the acetabulum.

The relative extent to which the head remains covered by a congruent acetabulum is believed by most authors to determine the ultimate prognosis. If lateral cxtrusion of the head has been minimal, the prognosis is belicved to bc good. The head may become quite large relative to the socket (coxa magna) or grossly distorted (malum

coxae juvenilis) and the prognosis is more guarded. Several studies have been directed toward the development of roentgenographic criteria for assessing the end results,[27,38,63,65,66] but no one has conclusively demonstrated a relationship between minor morphologic deviations and long-term functional disability.

One additional, somewhat unusual complication must be mentioned for completeness. This is osteochondritis dissecans,[38,39,56,67] which may form a loose body requiring removal just as the same process does in other joints.

Treatment

Opinions concerning the value of treatment for Legg-Perthes disease should be judged in light of several important observations.

- No controlled study has ever demonstrated a statistically significant difference between a treated group, regardless of the type of treatment

Figure 1.—Anteroposterior roentgenogram of the hips of a nine-year-old caucasian boy after the insidious onset of limp. The joint space on the left is somewhat increased, but there are no striking changes visible in the femoral heads themselves.

Figure 2.—Frog-leg lateral roentgenogram taken at the same time as Figure 1, showing minimal patches of sclerosis and cystic areas in the subchondral bone of the heads.

Figure 3.—Frog-leg lateral film of the hips, taken 13 months later, of the same boy shown in Figures 1 and 2. Sclerosis of the capital femoral epiphyses of both hips is now evident, and fragmentation is beginning.

Figure 4.—Frog-leg lateral view of the right hip of a nine-year-old boy. Rather pronounced mottling of the epiphysis is apparent. This is characteristic of the reparative stage, and the radiolucent areas represent ingrowth of granulation tissue. The head is now regaining strength; in this patient the anatomic form was maintained throughout. (See Figures 6 and 7.)

Figure 5.—Anteroposterior view of the hips of an 11-year-old boy with bilateral involvement. The right hip shows gross changes with extrusion of the head laterally, flattening of the lateral portion of the epiphysis, and broadening of the neck. Malum coxae juvenilis is developing in this hip, and the prognosis is guarded because of loss of congruence of the joint surfaces. On the left the joint remains congruent, but the head is large—the so-called coxa magna. The prognosis is better.

Figure 6.—Anteroposterior view of the left hip of the same patient whose right hip is shown two years earlier in Figure 4. The process has now healed with maintenance of the anatomic configuration of the head except for the formation of an asymptomatic osteochondritis dissecans. This is a somewhat unusual complication.

Figure 7.—Lateral view of the same hip seen in Figure 6. The osteochondritis dissecans is again visible in its bed, but the bony trabeculae of the remainder of the head are normal. Contrast this appearance with the increased density seen in Figure 3 and the mottling seen in Figure 4.

employed, and an untreated group. One recent study[57] indicated no significant difference between treated and untreated groups on follow-up evaluation after an average of ten and a half years.

- All treatment regimens for conditions which lend themselves poorly to controlled studies tend to follow disturbingly cyclic vogues of management, usually based on a current concept of pathogenesis.
- Treatment of Legg-Perthes disease presents a classic example of less than critical adoption of a wide variety of treatment methods, both conservative and surgical, and yet the question of treatment remains unresolved.[68,69]

Bed rest was first advocated as a treatment in 1934,[70] with or without splints or some type of traction.[39,71-73] It also was advocated with confidence, if not enthusiasm, during the 1950's and 1960's, while other approaches to treatment[31,38,74-76] allowed the patient to walk with "weight-relieving" devices such as crutches, walking calipers (patten-bottom braces), Sam Browne belts, Snyder's slings, and Thomas splints, with a built-up shoe on the foot opposite to the involved hip. Later such devices were shown to be only marginally effective at best in reducing intra-articular pressures in the hip. It was found that simple straight-leg raising while lying supine loads the femoral head with the same force as walking. This fact further confused the various rationales of treatment. Bed rest as a means of management has also been quietly retired, with no one able to show conclusively that the cost in money and confinement produces the desired results.

Tetracycline administered daily in small doses[77] has not been shown to influence the outcome in spite of an early report that it did. Indeed, no medication seems to influence the outcome in any way.

The current theory of pathogenesis is that the biologically plastic avascular head becomes subluxed and laterally extruded, thus permitting recurring forces from the acetabular rim[15,16,78,79] to deform the superior surface of the spherical head. It is then postulated that weight-bearing with the head completely contained within the acetabulum will allow concentric reformation of the plastic head.[80] The inference is that the congruence of joint surfaces thus obtained will be unlikely to result in subsequent degenerative joint disease. Several papers and much unpublished discussion in the past few years have dealt with the use of various abduction-internal rotation casts and braces designed to hold the head centered in the socket. Formerly, weight-bearing was not permitted.[58,81] The present tendency is to allow full weight-bearing in the device, provided the head is completely covered, on the theory that congruent deformation between head and socket is acceptable.[80,82,83] Unfortunately, no controlled data are yet available. Moreover, the percentage of good results in the largest study[80] looks disturbingly like that from other, untreated groups.[57]

Other investigators[17,50,78,79,84,85] have advocated subtrochanteric osteotomy to seat the head within the acetabulum, but even proponents of operation feel that its use should be limited to patients over six years of age in whom there is involvement of the whole head or with wide subluxation of the head and elevation of the lateral margin of the acetabulum. Innominate osteotomy, again for the purpose of better covering the head, also has its proponents.[86-88] Procedures designed to facilitate revascularization of the ischemic head, such as drilling or cancellous bone grafting of the necrotic head, have also been attempted.[89,90] Statistical confirmation of the belief that any of these measures does indeed alter the course of the process unfortunately is still lacking.

We are thus left with two unsatisfying conclusions. The prime cause of Legg-Perthes disease, although involving a vascular mechanism, remains unidentified. As is usually the case when the cause is not clear, effective treatment is also elusive. It appears at present that the ultimate solution to the problem of management may be related to revascularization of the head, but no one has yet been able to show this convincingly in any group of patients. Indeed, if such a technique could be developed it would have important applications in other fields, such as fracture healing and avascular necrosis of the femoral head of diverse causes in adults, where the condition is not self-limiting as it is in children. At present, however, all such efforts must be considered experimental and should not be attempted except under controlled conditions. In the meantime the practitioner is faced with a therapeutic problem in which the wisest course consists of doing the least harm while attempting to protect the femoral head from gross malformation.

At the University of California, San Francisco, we have been using abduction-internal rotation devices while keeping the patient ambulatory on crutches. We are doing this although we recognize the need for controlled studies with sufficient

patients to allow statistically meaningful conclusions. Because Legg-Perthes disease is not common enough to permit rapid accumulation of such data in any one center, the need for a cooperative protocol is clear.

REFERENCES

1. Calvé PJ: Forme particulière de pseudo-coxalgie—Greffée sur des déformations charactéristiques de l'extrémité supérieure du fémur. Rev Chir 42:54-84, 1910

2. Legg AT: An obscure affection of the hip-joint. Boston Med Surg J 162:202-204, 1910

3. Perthes: Uber arthritis deformans juvenilis. Dtsch Z Chir 107:111-159, 1910

4. Axhausen G: Klinische und histologische Beiträge zur Kenntnis der juvenilen Arthritis deformans coxae. Charité-Ann 33:414-422, 1909

5. Baker WM: Epiphysal necrosis and its consequences. Br Med J 2:416-419, 1883

6. Wright GA: On the value of determining the primary lesion in joint-disease as an indication for treatment. Br Med J 2:419-422, 1883

7. Waldenström H: Der obere tuberkulöse Collumherd. Z Orthop Chir 24:487-512, 1909

8. Helbo S: Morbus Calvé-Perthes. Odense, Denmark, Fyns Tidendes Bogtrykkeri, 1953

9. Molloy MK, MacMahon B: Birth weight and Legg-Perthes disease. J Bone Joint Surg 49-A:498-506, April 1967

10. Zemansky AP Jr: The pathology and pathogenesis of Legg-Calvé-Perthes' disease. (Osteochondritis juvenilis deformans coxae). Am J Surg 4:169-184, 1928

11. Jonsäter S: Coxa plana—A histo-pathologic and arthrographic study. Acta Orthop Scand, Suppl 12, 1953

12. Yamaguchi M: Histologic study on the neck of the femur in Perthes disease. Acta Med (Fukuoka) 29:317-332, 1959

13. Trueta J: Studies of the Development and Decay of the Human Frame. Philadelphia, W. B. Saunders Co., 1968

14. Kemp HBS: Avascular necrosis of the femoral head in dogs. J Bone Joint Surg 50-B:431, May 1968

15. Salter RB, Bell M: The pathogenesis of deformity in Legg-Perthes disease—An experimental investigation. J Bone Joint Surg 50-B:436, May 1968

16. Katz JF: Legg-Calvé-Perthes disease—The role of distortion of normal growth mechanisms in the production of deformity. Clin Orthop 71:193-198, 1970

17. Somerville EW: Perthes' disease of the hip. J Bone Joint Surg 53-B:639-649, Nov 1971

18. Dolman CL, Bell HM: The pathology of Legg-Calvé-Perthes disease—A case report. J Bone Joint Surg 55-A:184-188, Jan 1973

19. Nagura S, Kosuge S: Die Pathogenese und das Wesen der Perthesschen Krankheit (Experimentelle Beiträge zur Entstehung der Perthesschen Krankheit). Arch Klin Chir 191:347-371, 1938

20. Caffey J: The early roentgenographic changes in essential coxa plana—Their significance in pathogenesis. Am J Roentgenol 103:620-634, 1968

21. Tachdjian MO, Grana L: Response of the hip joint to increased intra-articular hydrostatic pressure. Clin Orthop 61:199-212, 1968

22. Gledhill RB, McIntyre JM: Transient synovitis and Legg-Calvé-Perthes disease—A comparative study. Can Med Assoc J 100:311-320, 1969

23. Salter RB: Perthes disease—Instructional Course Lecture, The American Academy of Orthopaedic Surgeons, Annual Meeting, Chicago, 1970

24. Jacobs BW: Synovitis of the hip in children and its significance. Pediatrics 47:558-566, 1971

25. Hipp E: Die Gefässe des Hüftkopfes—Anatomie, Angiographie und Klinik. Stuttgart, Ferdinand Enke, 1962

26. Nishio A, Yakushiji K: Legg-Calvé-Perthes disease—Histology and treatment. Yonago Acta Med 6:1-6, 1962

27. Goff CW: Legg-Calvé-Perthes Syndrome and Related Osteochondroses of Youth. Springfield, Ill., Charles C Thomas, 1954

28. Giannestras N: Legg-Perthes disease in twins. J Bone Joint Surg 36-A:149-152, Jan 1954

29. Ruckerbauer GM: Genetical factors in Legg-Perthes disease. Thesis, University of Toronto, 1955

30. Söderberg L: Simultaneous occurrence of coxa plana in enzygotic twins. Acta Orthop Scand 27:135-140, 1957

31. Wansbrough RM, Carrie AW, Walker NF, Ruckerbauer G: Coxa plana, its genetic aspects and results of treatment with the long Taylor walking caliper—A long-term follow-up study. J Bone Joint Surg 41-A:135-146, Jan 1959

32. Dunn AW: Coxa plana in monozygotic male twins. J Bone Joint Surg 42-A:178-183, Jan 1960

33. Inglis A: Genetic implications in coxa plana. J Bone Joint Surg 42-A:711-715, Jun 1960

34. Tracy HW: Coxa plana in siblings. NC Med J 24:76-79, 1963

35. Bernbeck R: Perthes-Leiden bei eineiigen Zwillingen. Z Orthop 103:299-308, 1967

36. Ryder CT, LeBouvier JD, Kane R: Coxa plana. Pediatrics 19:979-992, 1957

37. Cameron JM, Izatt MM: Legg-Calvé-Perthes' disease. Scott Med J 5:148-154, 1960

38. Mose K: Legg-Calvé-Perthes' Disease—A Comparison Between Three Methods of Conservative Treatment. Copenhagen, Universitetsforlaget 1 Aarhus, 1964

39. Edgren W: Coxa plana—A clinical and radiological investigation with particular reference to the importance of the metaphyseal changes for the final shape of the proximal part of the femur. Acta Orthop Scand, Suppl 84, 1965

40. Kemp HS, Boldero JL: Radiological changes in Perthes' disease. Br J Radiol 39:744-760, 1966

41. Taussig G. Héripret G: Maladie de Legg-Perthes-Calvé—A propos de 275 cas. Importance des facteurs mécaniques. Intérêt du traitement chirurgical. Rev Chir Orthop 55:305-330, 1969

42. Trueta J: The normal vascular anatomy of the human femoral head during growth. J Bone Joint Surg 39-B:358-394, May 1957

43. Adams JA: Transient synovitis of the hip joint in children. J Bone Joint Surg 45-B:471-476, Aug 1963

44. Monty CP: Prognosis of 'observation hip' in children. Arch Dis Child 37:539-542, 1962

45. Weiner DS, O'Dell HW: Legg-Calvé-Perthes disease—Observations on skeletal maturation. Clin Orthop 68:44-49, 1970

46. Girdany BR, Osman MZ: Longitudinal growth and skeletal maturation in Perthes' disease. Radiol Clin North Am 6:245-251, 1968

47. Fisher RL: An epidemiological study of Legg-Perthes disease. J Bone Joint Surg 54-A:769-778, Jun 1972

48. Sarpyener MA: Spina bifida aperta and congenital stricture of the spinal canal. J Bone Joint Surg 29:817-821, July 1947

49. Wilk LH: Juvenile osteochondrosis of the hip—Critical evaluation of pathogenesis and treatment. JAMA 192:939-946, 1965

50. Craig WA, Kramer WG, Watanabe R: Etiology and treatment of Legg-Calvé-Perthes syndrome. J Bone Joint Surg 45-A: 1325-1326, Sep 1963

51. Katz JF: Arthrography in Legg-Calvé-Perthes disease. J Bone Joint Surg 50-A:467-472, Apr 1968

52. Goff CW: Legg-Calvé-Perthes syndrome (LCPS)—An up-to-date critical review. Clin Orthop 22:93-107, 1962

53. Gower WE, Johnston RC: Legg-Perthes disease—Long-term follow-up of thirty-six patients. J Bone Joint Surg 53-A:759-768, Jun 1971

54. Eaton GO: Long-term results of treatment in coxa plana—Follow-up study of eighty-eight patients. J Bone Joint Surg 49-A: 1031-1042, Sep 1967

55. Danielsson LG, Hernborg J: Late results of Perthes' disease. Acta Orthop Scand 36:70-81, 1965

56. Ratliff AHC: Osteochondritis dissecans following Legg-Calvé-Perthes' disease. J Bone Joint Surg 49-B:108-111, Feb 1967

57. Catterall A: Natural history of Perthes' disease. J Bone Joint Surg 53-B:37-53, Feb 1971

58. Katz JF: Conservative treatment of Legg-Calvé-Perthes disease. J Bone Joint Surg 49-A:1043-1051, Sep 1967

59. Kemp HBS, Cholmeley JA, Baijens JK: Recurrent Perthes' disease. Br J Radiol 44:675-681, 1971

60. Katz JF: Recurrent Legg-Calvé-Perthes disease. J Bone Joint Surg 55-A:833-836, Jun 1973

61. Waldenström H: The definite form of the coxa plana. Acta Radiol 1:384-394, 1922

62. Brailsford JF: Avascular necrosis of bone. J Bone Joint Surg 25:249-260, Apr 1943

63. Heyman CH, Herndon CH: Legg-Perthes disease—A method for the measurement of the roentgenographic result. J Bone Joint Surg 32-A:767-778, Oct 1950

64. Schiller MG, Axer A: Legg-Calvé-Perthes syndrome (L.C.-P.S.)—A critical analysis of roentgenographic measurements. Clin Orthop 86:34-42, 1972

65. Eyre-Brook AL: Osteochondritis deformans coxae juvenilis or Perthes' disease—The results of treatment by traction in recumbency. Br J Surg 24:166-182, 1936

66. Sjövall H: Om Perthes sjukdom, dess diagnos och behandling. Svenska Läkartidn 40:214, 1943

67. Stillman BC: Osteochondritis dissecans and coxa plana—Review of the literature, with a personal case report. J Bone Joint Surg 48-B:64-81, Feb 1966

68. Holdsworth FW: Epiphyseal growth—Speculations on the nature of Perthes's disease. Ann R Coll Surg Engl 39:1-16, 1966

69. Daymond KR: Late results of Perthes' disease. J Bone Joint Surg 52-B:800, Nov 1970

70. Danforth MS: The treatment of Legg-Calvé-Perthes disease without weight-bearing. J Bone Joint Surg 16:516-534, Jul 1934

71. Meyer J: Treatment of Legg-Calvé-Perthes disease—Assessment of therapeutic results with particular reference to the value of traction in bed. Acta Orthop Scand, Suppl 86, 1966

72. Cumming WJ: A review of 100 cases of Legg-Calvé-Perthes' syndrome treated by recumbency. J Bone Joint Surg 49-B:386-387, May 1967

73. Karadimas JE: Conservative treatment of coxa plana—A comparison of the early results of different methods. J Bone Joint Surg 53-A:315-325, Mar 1971

74. Mindell ER, Sherman MS: Late results in Legg-Perthes disease. J Bone Joint Surg 33-A:1-23, Jan 1951

75. Evans DL, Lloyd-Roberts GC: Treatment in Legg-Calvé-Perthes' disease—A comparison of in-patient and out-patient methods. J Bone Joint Surg 40-B:182-189, May 1958

76. Herzog EG: A study of Perthes' disease—Preliminary report. Proc R Soc Med 54:1102, 1961

77. Goff CW: Influence of small daily doses of tetracycline on the clinical course of Legg-Calvé-Perthes syndrome—Report of a double-blind study. Clin Orthop 38:71-80, 1965

78. Axer A: Subtrochanteric osteotomy in the treatment of Perthes' disease—A preliminary report. J Bone Joint Surg 47-B: 489-499, Aug 1965

79. Axer A, Schiller MG: The pathogenesis of the early deformity of the capital femoral epiphysis in Legg-Calvé-Perthes syndrome (L.C.P.S.)—An arthrographic study. Clin Orthop 84: 106-115, 1972

80. Petrie JG, Bitenc I: The abduction weight-bearing treatment in Legg-Perthes' disease. J Bone Joint Surg 53-B:54-62, Feb 1971

81. Harrison MHM, Menon MPA: Legg-Calvé-Perthes disease —The value of roentgenographic measurement in clinical practice, with special reference to the broomstick plaster method. J Bone Joint Surg 48-A:1301-1318, Oct 1966

82. Harrison MHM, Turner MH, Nicholson FJ: Coxa plana—Results of a new form of splinting. J Bone Joint Surg 51-A:1057-1069, Sep 1969

83. Tachdjian MO: Pediatric Orthopedics. Philadelphia, W. B. Saunders Co, 1972

84. Somerville E: Perthes' disease. J Bone Joint Surg 50-B:885, Nov 1968

85. Oyston JK: Varus osteotomy for Perthes' disease. J Bone Joint Surg 51-B:387, May 1969

86. Canale ST, D'Anca AF, Cotler JM, Snedden HE: Innominate osteotomy in Legg-Calvé-Perthes disease. J Bone Joint Surg 54-A:25-40, Jan 1972

87. Litton LO: The use of innominate osteotomy in Legg-Perthes disease. Clin Orthop 85:295-296, 1972

88. Salter RB: Operative treatment of Perthes' disease—Current concepts in children's orthopaedics. American Academy of Orthopaedic Surgeons Instructional Course, Seattle, Washington, 1972

89. De Camargo FP: Revascularization of the neck of the femur in Legg-Calvé-Perthes syndrome—A new surgical technic—Experience of 80 cases. Clin Orthop 10:79-86, 1957

90. Cathro AJM, Kirkaldy-Willis WH: Treatment of Perthes' disease of the hip by cancellous bone grafting—Preliminary report. J Bone Joint Surg 45-B:284-291, May 1963

Cocaine Abuse

Recently there has been a considerable increase in frequency of cocaine abuse in the United States. Reasons for this are not clear but may be related in part to several factors: A relatively greater difficulty in obtaining heroin from Europe, a crackdown on the black market in amphetamines (which greatly resemble cocaine in their pharmacological effects), improved smuggling techniques from the South American sources, increased diversion from legitimate use of the United States production, and—by no means least important—a return of cocaine to fashion.

Cocaine is considered by users to produce an ideal "high" (elation) with prolongation and enhancement of sexual pleasure, an important (if uncertain) component. There are few drug users more preoccupied and emotionally involved with their habits than those who use cocaine. They are enthusiastic proselytizers for the drug.

Long defined as a powerfully addicting substance, cocaine is nevertheless quite different from the opiates in this respect. Habituation to, and craving for, cocaine are powerful. However, there is much less development of tolerance to cocaine than to most addicting drugs, even including amphetamines. Furthermore, the withdrawal syndrome, even after prolonged cocaine use, is considerably less dramatic than that seen upon withdrawal from opiates. Nevertheless, the characteristic prolonged sleep, lassitude, hunger, and particularly the great subjective sense of apathy, fatigue, and depression do constitute a significant withdrawal syndrome.

The cocaine addict's major psychiatric symptoms result from prolonged periods of intoxication by the drug, which is taken repeatedly to sustain the desired sense of exhilaration and euphoria that it produces, and to avoid the depression of withdrawal. A toxic picture develops, often with vivid hallucinations (visual, auditory and tactile) and delusional thought patterns, frequently paranoid in content. The mood is often elevated although there may be considerable lability, with outbursts of rage and periods of irritability. The user experiences a sense of great physical and mental vigor, together with hyper-alertness and loss of need for sleep, which often leads to a clinical picture of exhaustion overridden by the artificial stimulation of the drug. Crawling sensations (formications) on the skin are very common; scratch marks and excoriations are often seen and the user may be convinced that he is being attacked by insects. Otherwise, the clinical picture is similar in many ways to that seen in amphetamine addicts, although the psychotic syndrome develops more rapidly with cocaine as a rule.

Most cocaine users sniff the drug. Prolonged abuse often leads to lesions of the nasal mucosa because of the marked vasoconstriction and local anesthesia produced by cocaine. Those who sniff for many years are known to develop severe ulcerations of the nasal mucosa, sometimes leading to holes in the septum. With the recent adoption of cocaine use by members of the smart set, it is now not uncommon to see women at parties with gold or silver cocaine snifters (small double spoons capable of carrying a pinch of the drug to both nostrils) worn around the neck on a chain as an ornament.

Louis Jolyon West, MD

REFERENCES

Woods JH, Downs CA: The psychopharmacology of cocaine. National Commission on Marijuana and Drug Abuse, Washington DC, 1973

Fraenkel F, Joel E: Cocainism. Berlin, 1924

Specialty Conference

Participants

WILLIAM F. FRIEDMAN, MD
PAUL T. PITLICK, MD

Taken from the weekly Pediatric Grand Rounds held at the University Hospital of San Diego County, University of California, San Diego, School of Medicine, February 27, 1973

Refer to: Friedman WF, Pitlick PT: Ventricular septal defect in infancy—University of California, San Diego (Specialty Conferences). West J Med 120:295-300, Apr 1974

Ventricular Septal Defect in Infancy

DR. PITLICK:* The patient we are discussing this morning was born after a full-term, uncomplicated pregnancy and delivery. His course in the Newborn Nursery was uneventful, and physical examination on discharge was within normal limits. He did well until he was about six weeks of age, when, on routine examination, his private physician heard a heart murmur. Later his parents noticed that he ate poorly and was often diaphoretic. At seven weeks of age he was referred to the Pediatric Cardiology Clinic at University Hospital, where a clinical diagnosis of ventricular septal defect was made. When he was three months old, treatment was begun with digitalis.

At six and a half months he was admitted to University Hospital for evaluation of tachypnea, diaphoresis, and weight loss. In the two weeks before admission he had lost 11 ounces. Although he had weighed 5 pounds, 10 ounces at birth, both his weight gain and linear growth were so slow that at the time of admission he weighed only 7 pounds, 10 ounces.

On physical examination the patient was irritable. The respiratory rate was 60 to 70 and the heart rate 135 per minute. Blood pressure in arms and legs was within normal limits. The precordium was active, with a 2 plus right ventricular lift and a 2 plus left ventricular heave. A systolic thrill was felt over the lower left precordium. The first heart sound was normal. The second was split narrowly, with an accentuated pulmonic component. No third or fourth heart sound was audible, nor was an ejection sound heard. A widely radiated, grade IV/VI, harsh, holosystolic murmur was heard best at the third left interspace and left sternal border. A grade II/VI mid-diastolic rumble was heard at the lower left sternal border. The liver was 3 cm below the right costal margin. The spleen was not palpated.

An electrocardiogram showed an axis of plus 90 degrees. The P waves in lead II were broad, and in lead VI showed a large terminal negative component, indicative of left atrial enlargement. Combined ventricular hypertrophy was also present. The vectocardiogram also illustrated the findings of combined ventricular hypertrophy. A phonocardiogram showed the holosystolic nature of the systolic murmur and the mid-diastolic flow murmur.

A frontal chest x-ray film showed striking cardiomegaly with biventricular enlargement. The increase in pulmonary vascularity was consistent with a large left-to-right shunt. With barium in the esophagus, left atrial enlargement was evident. The combination of biventricular and left atrial enlargement with increased pulmonary vascularity was thought to be compatible with a left-to-right shunt at the ventricular level.

*Fellow in Pediatric Cardiology, supported by Training Grant HDO 0335 from the National Institutes of Health.

Reprint requests to: W. H. Friedman, MD, Division of Pediatric Cardiology, University Hospital of San Diego County, 225 West Dickinson St., San Diego, CA 92103.

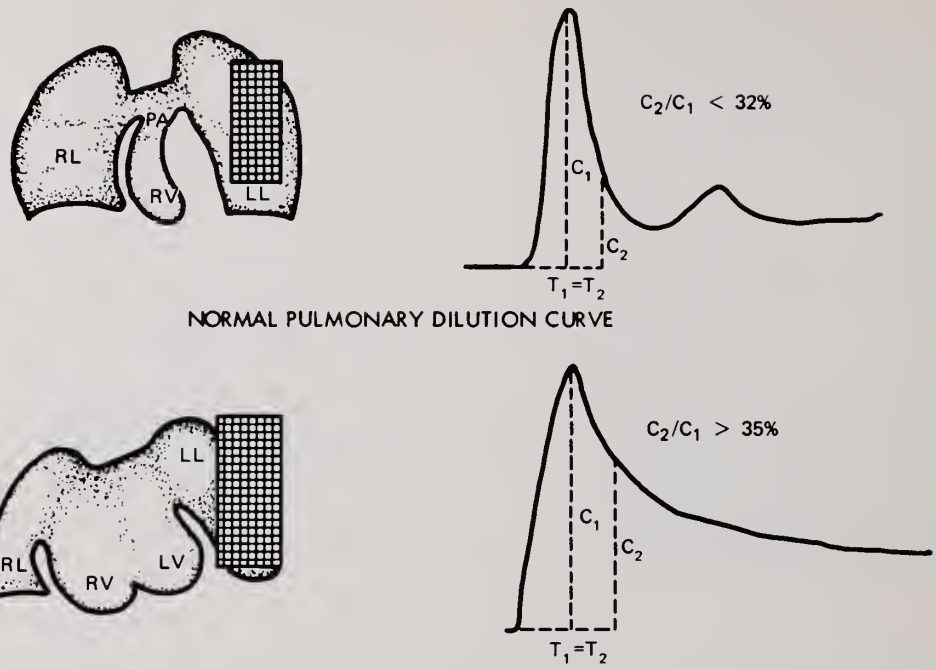


Figure 1.—Top: Normal pulmonary radionuclide dilution curve. The image on the right ventricle (RV) and lungs (RL, LL) represents one selected frame from among many sequential, 0.5 second exposures made following injection of the bolus via a central venous catheter into the superior vena cava. Each dot in the playback image now represents a discrete location in a computer's core memory from which time-sequential information may be extracted. The intensified rectangular area over the left lung (LL) was chosen as the region from which the time-activity curve (top right) was generated. The computer automatically examined each 0.5 second frame, added all counts from within the region of interest over the left lung, and displayed the sums vertically along the horizontal time axis. Note the rapid drop in the count rate as the bolus leaves the lung region intact—that is, without an immediate recirculation from the left side of the heart. The descending slope is described as the ratio of the two **count** rates, C_1 and C_2, at **times** T_1 and T_2 respectively. T_1 corresponds to the time from the beginning of the ascending slope to the maximum count rate, and T_2 is an equal period of time, as shown. **Bottom:** Left-to-right shunt. This curve, produced in the same way as above, shows a slow decline in count rate (prolonged downslope) caused by the recirculation of a portion of the radioisotope bolus back to the pulmonary circulation, having been shunted through an atrial septal defect. The elevated C_2:C_1 ratio indicates that a left-to-right shunt of significant magnitude is present, but it does not localize the site of the shunt.

A radioisotope angiocardiogram was made. After an intravenous injection of technetium-99 into a peripheral vein, Polaroid photographs were taken as it circulated through the heart and lungs.

In the course of this procedure, the output of the gamma camera is simultaneously recorded on digital magnetic tape so that an anatomic area of interest may be reviewed later. By setting the area of interest as a peripheral portion of lung, we can, with computer assistance, generate an analog curve of the appearance and disappearance of the isotope counts in that area. The resulting pulmonary vascular dilution curve shows the time-to-activity relationship of the flow of radioisotope through the lung. It is analogous to the indicator-dilution curves inscribed with indocyanine green at cardiac catheterization. From the curve, a C_2:C_1 ratio is calculated. C_1 is the point of peak activity, and C_2 is a point on the curve which occurs at twice the time from the moment of the appearance of the radioactivity to C_1. Normal curves show a prompt rise to peak and a prompt fall, giving a C_2:C_1 ratio of less than 34:100 (Figure 1). In patients with left-to-right shunts, because of the recirculation of blood through the lungs via the shunt the descending

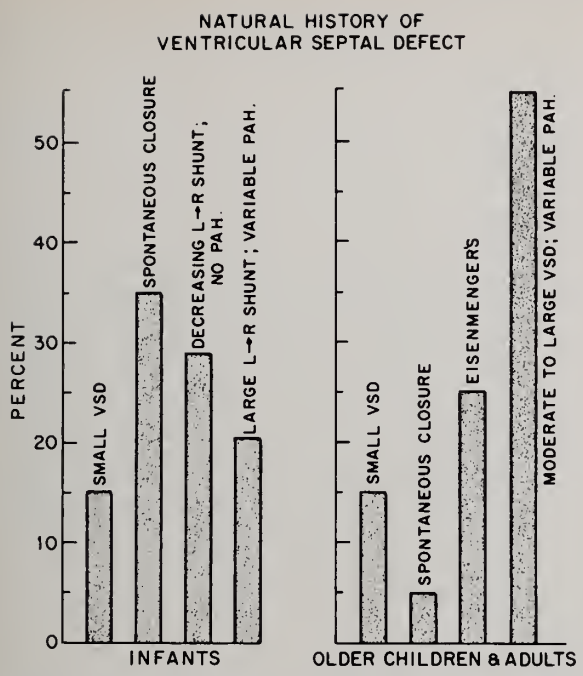


Chart 1.—The incidence of the small ventricular septal defect (VSD) is similar in populations of infants and older patients. Spontaneous closure is far more common in infants, while the fully developed Eisenmenger's reaction (net right-to-left shunt, inoperable) is rare in infancy, although pulmonary arterial hypertension (PAH) occurs and may progress rapidly.

limb of the curve becomes abnormally prolonged, giving a high C_2 value and an abnormally high C_2:C_1 ratio. In our experience the C_2:C_1 ratio has always been higher than 35:100 in children with a left-to-right shunt. The pulmonary vascular dilution curve of this patient showed a C_2:C_1 ratio of 50:100 (Figure 1).

I want to emphasize that the isotope technique is of lesser value in a patient like the one we are discussing today, in whom a large left-to-right shunt was apparent clinically than it is in patients in whom the existence of a left-to-right shunt is not obvious. This technique permits distinction between an innocent heart murmur and one due to a small ventricular septal defect.

At hemodynamic study of this patient, a catheter was passed into the right atrium where the oxygen saturation was found to be 60 percent. A pressure of 92/7 mm of mercury was measured in the right ventricle, with oxygen saturation of 86 percent. The saturation was also 86 percent in the pulmonary artery, and pressure was close to systemic. Left heart cathetherization was done retrograde from the brachial artery. Oxygen saturation of 98 percent was measured in the aorta, and pressure there was 96/70 mm. No pressure gradient existed between the aorta and left ventricle, and oxygen saturation in the left ventricle was normal. A pulmonary:systemic flow ratio of 3:1 and a normal pulmonary:systemic resistance ratio were calculated. Thus our patient had a ventricular septal defect and hyperkinetic pulmonary hypertension. Angiocardiography confirmed the presence of ventricular septal defect and did not demonstrate patent ductus arteriosus.

Dr. Friedman:* Pronounced failure to thrive such as was observable in this patient is one of the indications for operation early in life. The other indications include refractory congestive failure, persistent pulmonary infections, and the onset of vascular obstructive changes in the pulmonary bed. Consequently this patient was taken to the operating room where a pulmonary arterial banding procedure constricted the vessel sufficiently to reduce the pressure to 30 mm of mercury. Obviously one hopes to create a balanced shunt situation after banding. Too much constriction produces tetralogy of Fallot physiology; insufficient banding permits a large left-to-right shunt to persist.

Our patient's operation was quite successful. Weight gain accelerated and he became generally less irritable.

I would like to make some general remarks about ventricular septal defect and to bring out some of the physiological variables that are important in determining the clinical presentation. I want to emphasize that this particular lesion is the most common of all cardiac malformations. Almost every pediatrician or general practitioner will encounter several children with a ventricular septal defect at some time in his practice. Charts 1 and 2 summarize a large amount of information recently collected concerning the natural history and complications of this defect.

It is unusual for a ventricular septal defect to cause difficulties at birth, although congestive heart failure during the first year of life is a frequent occurrence. Diagnosis during the neonatal period is therefore extremely helpful in order to assure more careful observation of the affected infant. The examining physician usually suspects the diagnosis from the presence of a harsh systolic murmur at the lower left sternal border. Electrocardiograms and chest x-ray studies of these infants are within normal limits in the im-

*Professor of Pediatrics and Chief, Division of Pediatric Cardiology, Recipient of USPHS Research Career Development Award 5K04 HL 41737 from the National Heart and Lung Institute.

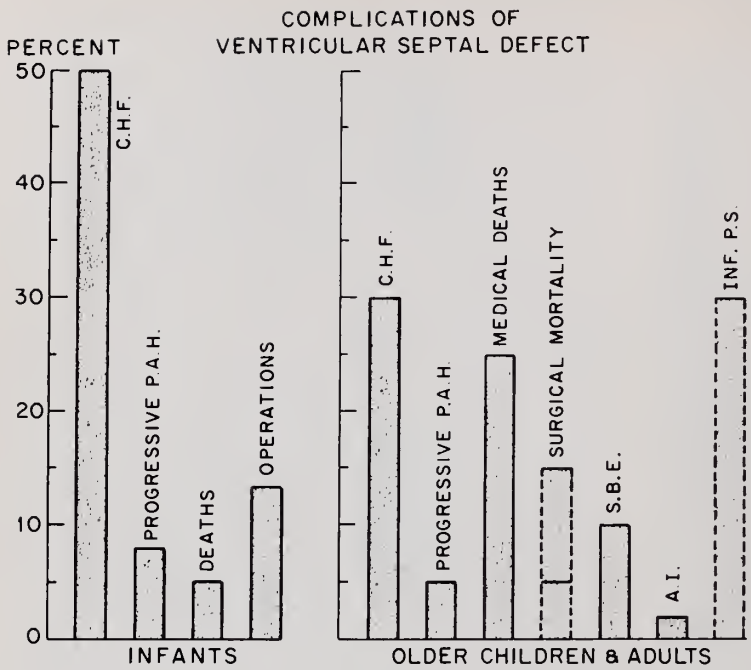


Chart 2.—Congestive heart failure (CHF) is frequent at all ages. Medical and surgical deaths are more common in older patients with large defects and pulmonary arterial hypertension (PAH). The surgical mortality in various series ranges from 0 to 15 percent. Subacute bacterial endocarditis (SBE) is rare in infancy. Aortic insufficiency (AI) is a rare occurrence. Infundibular pulmonary stenosis (Inf. PS) may develop in some patients, but in most instances some obstruction is present initially and may be progressive.

mediate neonatal period because appreciable left-to-right shunting occurs only after the pulmonary vessels lose their fetal characteristics and pulmonary vascular resistance decreases. These infants should be seen more frequently for well-baby care. The baby whose ventricular septal defect either decreases in size or closes completely during the first year of life presents no problem. In contrast, if a moderate or large defect is present, the net left-to-right shunt will increase during the first months of life as pulmonary vascular resistance falls. Examination during this time usually reveals a thrill along the lower left sternal border, and the holosystolic murmur of flow across the interventricular defect may be accompanied by a diastolic flow rumble across the mitral valve. Chest x-ray films begin to show increased pulmonary vascular markings, and left or biventricular hypertrophy may become evident from electrocardiograms. Infants with a large left-to-right shunt tend to do poorly and have recurrent upper and lower respiratory infections, failure to gain weight, and congestive heart failure. The congestive heart failure may be severe and intractable despite intensive medical management with digitalis, diuretics, sodium restriction, and oxygen. For these infants we recommend surgical banding of the pulmonary artery in order to reduce pulmonary blood flow and to alleviate the heart failure. When this operation is successful, sufficient growth ensues and the patient becomes a candidate for corrective operation later on. Because of advances in cardiopulmonary bypass and in infant intracardiac surgery, we reserve banding procedures for infants less than six months of age who weigh less than 12 or 14 pounds. Older or larger patients are candidates for total operative correction. Fortunately, medical treatment is often successful in controlling the congestive heart failure. Nevertheless, these infants should still be referred for cardiac catheterization to permit evaluation of the degree of pulmonary arterial hypertension and of any associated defects such as patent ductus arteriosus or coarctation of the aorta which might require surgical correction.

The major concern of the pediatric cardiologist is to identify the patient in whom irreversible pulmonary vascular obstructive disease may develop (Eisenmenger reaction). Retrospective analyses of children who have had this complication indicate that infants with systemic or near-systemic pressure in the pulmonary artery at the time of initial hemodynamic study are at the greatest risk. Such infants need early recatheterization and serial determinations of the pulmonary vascular resistance in order to decide if surgical intervention is necessary to prevent the development of fixed, obliterative changes in the pulmonary vessels.

Beyond the first year of life, a variable clinical picture emerges in children with ventricular septal defect. If the defect is small, the child is usually

asymptomatic. The electrocardiogram is generally normal, and chest x-ray films show only a mild increase or normal pulmonary vascular markings. Effort intolerance and fatigue are associated with moderate left-to-right shunts. These children have cardiomegaly and a forceful left ventricular impulse and a prominent systolic thrill along the lower left sternal border. The second heart sound is normally split, with moderate accentuation of the pulmonic component; a third heart sound and a rumbling, diastolic murmur which reflects increased flow across the mitral valve are audible at the cardiac apex. The characteristic murmur which results from flow across the defect is harsh and holosystolic; it is best heard along the third and fourth interspaces to the left of the sternum and is widely transmitted over the precordium. A basal mid-systolic ejection murmur may also be heard because of increased flow across the pulmonic valve. The electrocardiogram is consistent with left or combined ventricular hypertrophy, and x-ray studies show cardiomegaly, left atrial enlargement, and increased vascular marking.

In some patients with a ventricular septal defect and a moderate to large left-to-right shunt early in life, the clinical picture may change with time to resemble more closely the findings observed in patients with tetralogy of Fallot. That is, subvalvular, right ventricular outflow obstruction develops and, depending on its severity, may ultimately result in reduced pulmonary blood flow and a right-to-left shunt across the ventricular septal defect. Operative correction in such patients often necessitates resection of subpulmonic tissue and insertion of a patch of prosthetic material to enlarge the outflow tract.

Less frequently, the physician may detect the early diastolic blowing murmur and wide pulse pressure of aortic regurgitation in a patient with a ventricular septal defect. This aortic regurgitation may become the predominant hemodynamic abnormality. In some of these children it appears to result from a primary abnormality of the aortic valve, while in others it may be caused by herniation of an aortic leaflet through the ventricular septal defect. Prosthetic aortic valve replacement may be necessary in the former patients, whereas closure of the ventricular septal defect may be all that is required in the latter group. Unfortunately, preoperative distinction of the two groups is difficult, and the management of patients with ventricular septal defect and aortic regurgitation is currently controversial.

It is rarely necessary to restrict the activity of a child with an isolated ventricular septal defect. Subacute bacterial endocarditis is always a threat, and antibiotic prophylaxis for dental procedures and minor surgical corrections is indicated (procaine penicillin, 600,000 units, supplemented by crystalline penicillin one to two hours before the procedure). An alternative regimen consists of oral administration of penicillin V, 0.25 gram, or penicillin G, 500,000 units every four to six hours times four doses on the day of and two days following the procedure, with an extra dose one hour before the manipulation. Respiratory infections require prompt evaluation and treatment. A child with an isolated ventricular septal defect should be seen once or twice yearly to detect clinical changes which may suggest that pulmonary vascular obliterative changes are developing.

If a child who previously had a loud murmur and thrill associated with poor growth suddenly has a growth spurt, fewer respiratory infections, and a decrease in the intensity of his murmur and disappearance of the thrill, it may be that severe changes are developing in the pulmonary vascular bed. An increase in the intensity of the pulmonic component of the second heart sound, a reduction in heart size as radiographically observed, and more pronounced right ventricular hypertrophy as indicated by the electrocardiogram are also frequent findings in such a case. These changes occur because the increased pulmonary vascular resistance causes a decrease in the left-to-right shunt. If these changes are suspected, cardiac catheterization should be repeated. If surgical repair is indicated, it should be undertaken promptly to prevent a predominant right-to-left shunt and inoperability.

It is unrealistic to state categorically the most appropriate age for elective hemodynamic evaluation and corrective operation. Of prime importance in the hemodynamic evaluation is the determination of pressure and blood flow in the pulmonary artery. We do not recommend surgical treatment for children with a small shunt—that is, one in which the ratio of pulmonary to systemic flow is less than 1.5:1—provided the pulmonary arterial pressure is normal. In these patients the remaining risk of subacute bacterial endocarditis does not exceed the risk of operation. Moreover, although the inherent risk of operation is small, the possibility of postoperative heart block, infection or other complications of

ventriculotomy and perfusion dictates a conservative approach when the cardiac defect is small enough to be well tolerated for life.

In children with larger shunts, operation may be advised before they enter school and are exposed to the multiple infections encountered in the schoolroom. On the other hand, there may be less psychological and physical morbidity in the older child who is often easier to work with in the postoperative period. A total assessment of the psychosocial dynamics of the family and the child are obviously helpful in determining the proper age for operation.

Occasionally one encounters a child in whom severe pulmonary vascular obstruction and a net right-to-left shunt across the defect have already developed. Symptoms may consist of exertional dyspnea, chest pain, syncope, and hemoptysis. The right-to-left shunt leads to cyanosis, clubbing, and polycythemia. At present there is little to offer this group of patients other than continuing support to the patient and his family.

Airway Obstruction in the Newborn

In newborn infants, serious obstruction may occur at any level from the nose to the alveoli. Infants with lower airway obstruction breathe rapidly, with sternal, subcostal and intercostal retractions. With upper airway obstruction, they exhibit deeper inspiratory efforts with suprasternal retractions as well. Inspiratory stridor is characteristic of glottic and supraglottic obstruction; expiratory stridor occurs with obstruction below the larynx. Weakness or absence of cry is associated with pathologic change at the vocal cord level. A brassy cough is indicative of subglottic or tracheal obstruction.

The nose, nasopharynx and pharynx should be examined for obstructive lesions. Catheters are passed through the nose to test for posterior choanal patency. The larynx is examined by direct laryngoscopy, without anesthesia, in search for vocal cord paralysis, subglottic stenosis, webs or cysts. If no obstruction is noted above the trachea, a 3.5 mm bronchoscope may be passed to examine for tracheal obstruction, usually from extrinsic compression from a vascular anomaly or a mass in the neck or the mediastinum.

After first insuring an adequate airway, one may then deal with the cause of the obstruction. With mild obstruction, careful observation may be all that is necessary. In more severe obstruction, intubation or tracheostomy may be indicated.

Bilateral choanal atresia may be fatal in the newborn, who has not yet learned to breathe through his mouth. Insertion of an oral airway may be lifesaving. Transnasal resection of the obstruction can be performed in the newborn.

In neonates with micrognathia, the tongue may obstruct the airway, especially when the infant is attempting to feed, or is sleeping on his back. Some can be managed by prone positioning, and careful feeding with a lambs' nipple, which is softer and has a larger opening than standard nipples. More severe cases require surgical operation to hold the tongue forward. The best procedure is construction of flaps between the lower lip and the inferior surface of the tongue.

The leading cause of lower airway obstruction is respiratory disease syndrome (RDS) caused by a deficiency of surfactant, the component that decreases surface tension in the alveolae. With insufficient surfactant, the infant's alveolae expand only with high inspiratory pressures; they then collapse on expiration. Infants with this condition are managed with positive pressure. This is by either continuous positive pressure ventilation (CPPV), or continuous positive airway pressure (CPAP).

Prolonged endotracheal intubation for RDS of the newborn, if polyvinyl chloride tubes are used, seldom results in the laryngeal complications often seen in older children and adults. Reasons for this are: Polyvinyl chloride softens at body temperature and exerts little pressure on the larynx; also the cartilages of the newborn larynx are relatively soft and yielding.

When the obstruction is due to laryngeal anomalies, tracheostomy is usually necessary. It should be performed over a bronchoscope or an endotracheal tube, when possible. Size 000 tracheostomy tubes are designed for prematures; 00 tubes are used in neonates over 5 or 6 pounds. Among the metal tracheostomy tubes, the 65 degree angle of the Holinger design fits better in most newborn necks than the 90 degree angle of Jackson cannulas. Plastic, or silastic, infant tracheostomy tubes are softer and more flexible; theoretically, they should cause less tracheal irritation. They have two disadvantages, however. They lack inner cannulas, and their flexibility increases the danger of accidental decannulation.

Alden H. Miller, MD, and Donald B. Hawkins, MD, *Los Angeles*

REFERENCES

Ferguson CF: Congenital abnormalities of the infant larynx. Otolaryngol Clinics North Am 3:185-200, Jun 1970

Gregory GA, Ketterman JA, Phibbs RH, et al: Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. N Engl J Med 284:1333-1339, Jun 17, 1971

Stool SE, Groff DB: Disposable plastic tracheostomy tubes. Laryngoscope 79:1088-1094, 1969

Refer to: Iatrogenic Cushing's syndrome—Medical Staff Conference, University of California, San Francisco. West J Med 120:301-306, Apr 1974

Medical Staff Conference

Iatrogenic Cushing's Syndrome

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. FORSHAM:* *The topic for discussion at Medical Grand Rounds this morning is exogenous Cushing's syndrome. It is a problem of widespread prevalence. The case which will be discussed concerns a problem which is of particular and increasing concern for people living in the western states. Dr. Steven Hindman will present the clinical description.*

DR. HINDMAN:† The patient is a 46-year-old housewife who, in 1961, began to note arthritic pains beginning in the feet and later spreading symmetrically to the wrists, fingers, neck, shoulders, knees and hips. She was given a brief course of aspirin without much relief. In 1967 a right carpal tunnel syndrome developed and surgical tunnel lysis was carried out. By 1968 the arthritis had become more severe and debilitating, and she had unsuccessfully sought relief from several physicians. Finally, on the advice of a friend she went to a doctor in Mexico who prescribed some "pink" tablets. Within two or three days of beginning this therapy she had dramatic and sustained relief. Within two weeks she also noted a remarkable increase in appetite and by the end of two months had gained approximately 20 pounds. She continued to be followed by the same doctor and in late 1972 and early 1973 began to notice changes which consisted of a fullness of her face, a rounding of the shoulders, a hump on her back, increased abdominal fat, and pain in the back and cervical spine.

In August 1973, while being admitted to another hospital for the evaluation of easy bruising, poor healing of minor abrasions, and gastrointestinal symptoms, she was noted to be grossly "Cushingoid." At that time her serum cortisol and urinary 17-hydroxycorticosteroid levels were very low. It was suspected that she was taking glucocorticoid medications, but her physician and the pharmacy in Mexico both repeatedly claimed that these tablets were indomethicin. However, when her prescribed tablets were replaced by the latter drug, there was a prompt recurrence of arthritis, and she also noted nausea, weakness and general discomfort.

She was first seen at the University of California, San Francisco, in November 1973. On admission the patient had typical features of Cushing's syndrome including truncal obesity, round facies, a buffalo hump, and thin arms and legs. Vital signs were normal, except for labile hypertension with blood pressure ranging between 175/115 and 110/80 mm of mercury. There were no

*Peter H. Forsham, MD, Professor of Medicine and Pediatrics and Director Metabolic Research Unit, University of California.
†Stephen H. Hindman, MD, Intern in Medicine.

abdominal striae, but there was increased abdominal fat and pronounced discomfort on direct percussion over the lumbosacral spine. The joints had palpably thickened synovia, but except in the wrists there was a full range of motion of all joints. The skin was thin and there were multiple ecchymotic patches and petechiae on the extremities. Mild proximal muscle weakness and mild atrophy of the quadriceps were noted.

Laboratory studies showed a normal concentration of hemoglobin, normal white blood cell count and differential, fasting blood sugar of 88 mg per 100 ml, and no detectable serum antinuclear antibody or rheumatoid factor. The erythrocyte sedimentation rate ranged between 14 and 25 mm in one hour (Westergren). The urinalysis and serum electrolytes, calcium, phosphorus and blood urea nitrogen were normal. An upper gastrointestinal series suggested the presence of gastric and duodenal ulcers. Bone x-rays revealed diffuse osteoporosis with multiple compression fractures of the vertebral bodies in the thoracic and lumbar spines. There were also typical arthritic changes in the carpals, metatarsals and phalanges, with cyst formation and erosions. Our initial impression was that she had rheumatoid arthritis and iatrogenic Cushing's syndrome.

DR. FORSHAM: *Dr. John Baxter will discuss this patient and her problem of glucocorticoid excess.*

DR. BAXTER:* This patient has a number of problems associated with glucocorticoid excess, and she does have iatrogenic Cushing's syndrome. In contrast to the spontaneous form of the disease, which is rarely or infrequently observed, iatrogenic Cushing's syndrome is quite common. It is estimated that in this country some 5,000,000 patients per year receive glucocorticoids for various reasons.[1] Of course, not all of the people become frankly Cushingoid, but the potential for the serious side effects of glucocorticoids is great. In addition to the fact that glucocorticoid treatment is common, the manifestations of glucocorticoid excess are such that iatrogenic Cushing's syndrome needs to be considered in the differential diagnosis of such common medical problems as obesity, impaired carbohydrate tolerance, hypertension, osteoporosis, and menstrual irregularities. Finally, this is a serious disease; in the era before treatment was available, patients with spontaneous Cushing's syndrome usually survived less than five years.[1]

*John D. Baxter, MD, Assistant Professor of Medicine and Lecturer in Biochemistry.

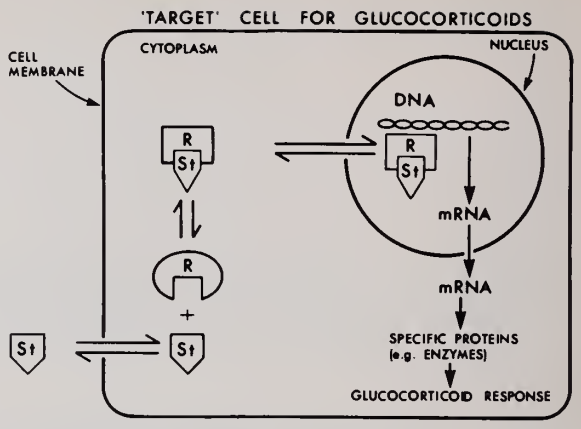


Chart 1.—Steps in glucocorticoid action. St = steroid; R = specific glucocorticoid receptor. The dissimilar shapes of R represent different conformations of R which depend on whether it is bound by the steroid. The steroid-bound and steroid-free forms of R differ in only the bound form associates with the cell nucleus. (Reprinted from Baxter and Forsham.[2])

The clinical manifestations are generally attributed to glucocorticoid excess. Many of the physiologic and biochemical mechanisms which produce these effects are poorly understood, nevertheless some general concepts are emerging and are useful to the physician considering the disease. First, most if not all of the physiologic effects of glucocorticoids are mediated through a common mechanism as is illustrated in Chart 1 (for review, see references 2 and 3). Briefly, the steroid enters its target cell and binds reversibly to specific cytoplasmic receptor proteins. This hormone-receptor complex then binds in the cell nucleus and in some way promotes an increased concentration of specific messenger ribonucleic acid (RNA). The latter codes for the production of specific proteins, many of which are enzymes. These proteins in turn elicit what we recognize as the glucocorticoid response.

Many of the physiological effects of the glucocorticoids are generally inhibitory, and many of the manifestations of Cushing's syndrome are due to these catabolic and antianabolic actions. Even when the gross effect on the cell and on the patient is catabolic, it still appears that the synthesis of macromolecules, as shown in Chart 1, is required to elicit the response, although we do not yet know which specific proteins or enzymes are responsible.[2,4]

An illustration of some of the tissues which are influenced by the glucocorticoids and the factors

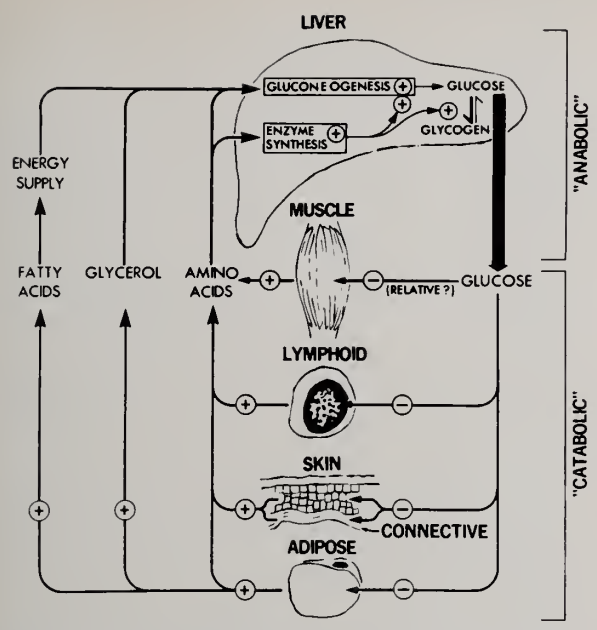


Chart 2.—Glucocorticoid actions on carbohydrate, lipid, and protein metabolism in various tissues. The + or − signs indicate stimulation or inhibition, respectively. (Reprinted from Baxter and Forsham.[2])

which ultimately produce many of the clinical manifestations of Cushing's syndrome is shown in Chart 2. There is an inhibition of glucose uptake in lymphoid cells, skin, connective tissue, and adipose tissue, and in these tissues and in muscle there is decreased uptake of amino acids.[2,4,5] In addition, there is a general inhibition of protein synthesis and an increased degradation of proteins, resulting in a release of amino acids. In adipose tissue, the steroids enhance lipolytic stimuli and thus release glycerol and fatty acids. The decrease in glucose uptake alone results in a tendency to hyperglycemia,[4] but in addition, the increased flux of amino acids and glycerol into the liver results in more glucose production, enhancing the tendency to hyperglycemia and impaired carbohydrate tolerance. The glucocorticoids stimulate the production of a number of enzymes in the liver, which in turn enhance the liver's gluconeogenic capacity.[2,5] In most people, as in this patient, the blood sugar is normal or nearly normal, apparently because the tendency to hyperglycemia is compensated for by hyperinsulinism.[5]

In contrast to the frequently compensated blood sugar, the catabolic actions of the glucocorticoids on tissues (some of which are shown in Chart 2) are much more devastating, especially when glucocorticoids are given in large excess. Table 1 lists some of the clinical manifestations of

TABLE 1.—*Clinical Features of Cushing's Syndrome Which Are Most Likely Promoted or Caused by the Catabolic and Antianabolic Actions of the Glucocorticoids*

Easy bruising, purpura
Poor wound healing
Striae or thinning of skin
Muscular weakness or wasting
Impaired carbohydrate tolerance
Poor resistance to infection
Osteoporosis
Lymphopenia
Eosinopenia

Cushing's syndrome which are probably due to these catabolic actions. Poor wound healing, easy bruising, purpura, and poor resistance to infection are predominantly due to glucocorticoid effects on the connective tissues, although actions on the lymphoid and immune systems also influence the course of infection. In fact, infection was the most common cause of death in Cushing's syndrome before surgical cure of the disease was possible.[1] The lowered resistance is toward viral, bacterial, parasitic, and fungal infections (especially tuberculosis). Osteoporosis is possibly the major problem of our patient, and is probably the major limitation to long-term glucocorticoid therapy. Although the pathogenesis of this condition is not clear and glucocorticoids produce a number of different effects on calcium metabolism, it is likely that inhibitory actions of the steroids on the bone matrix itself are responsible for development of this debilitating bone condition. Striae, thinning of the skin, lymphopenia and eosinopenia are probably due to direct effects on the respective tissue systems. Finally, patients with Cushing's syndrome develop myopathy and muscular weakness which is usually more of a proximal nature.[1] This was true of the patient presented this morning.

Other clinical manifestations of glucocorticoid excess (Table 2) have a less clear physiologic explanation. For example, there is a redistribution of fat. If, as mentioned above, glucocorticoids enhance the lipolytic stimuli, one would expect people with Cushing's syndrome to be thin; in fact they are frequently more obese. Two processes appear to contribute to the obesity: (1) glucocorticoids tend to increase the appetite; and (2) it is likely that the compensatory hyperinsulinism which promotes lipogenesis and inhibits lipolysis is having a more dominant effect than the glucocorticoids on the truncal areas where the obesity

TABLE 2.—*Relative Frequency of Clinical Features of Iatrogenic versus Spontaneous Cushing's Syndrome*

More Common in the Iatrogenic Syndrome	*Equal Frequency*	*More Common in the Spontaneous Syndrome*
Euphoria	Obesity	Hirsutism
Pseudotumor cerebri	Mental symptoms	Acne
Cataract	Edema	Menstrual disturbances
Pancreatitis	The Features listed in Table 1	Hypertension
Myopathy		Hypokalemia

is prominent, whereas the steroid effects are more dominant on the extremities.[1,2,5] Leukocytosis, although common, was not found in our patient. When present, it is probably the result of a direct effect of the glucocorticoid on mobilization of leukocytes from bone marrow.[2]

In addition to an increase in appetite, there is a frequent occurrence (40 to 50 percent of cases[1]) of emotional disturbance in both iatrogenic and natural Cushing's syndrome. A number of other glucocorticoid actions on the central nervous system have also been described.[1,2]

Our patient has both gastric and duodenal ulcers which have been associated with rheumatoid arthritis. Although there are reports of corticosteroid enhancement of the stimuli to gastric acid production and of steroid influence on the gastric secretions in other ways,[1,2] the association of peptic ulceration with iatrogenic or spontaneous Cushing's syndrome is controversial.[6]

There are notable differences between the iatrogenic and the spontaneous forms of Cushing's syndrome (Table 2), and these have been reviewed in detail by Christy.[1] Only in the spontaneous disease are hirsutism and acne seen, and they are probably due to the excess adrenal androgens which are produced in addition to the glucocorticoids.[1] Menstrual disturbances are probably more common in spontaneous Cushing's syndrome. This is due not only to the glucocorticoid inhibition of gonadotropin release but also to the adrenal androgens.[2] Hypertension and hypokalemia are more frequently seen in the spontaneous form of Cushing's syndrome than in the iatrogenic form.[1] The mechanisms for these differences are not clearly understood although explanations have been offered.[1] Pseudotumor cerebri, cataract, glaucoma and pancreatitis are manifestations of excess glucocorticoids and tend to be observed more in the iatrogenic form of the disease.[1] Reasons for (and even the existence of) an increased incidence of myopathy in the iatrogenic syndrome are not clear.

Laboratory values related to the adrenal-pituitary axis found in exogenous Cushing's syndrome (Table 3) depend on the responsible agent. If the patient has received ACTH or cortisol, then increased amounts of these substances should be found in plasma. However, the usual diurnal fluctuations are then missing, and thus blood or urine levels depend on the time of medication. The synthetic glucocorticoids such as prednisolone, betamethasone, triamcinolone or dexamethasone are generally not measured by current assays for cortisol, although in some instances they are weakly detected. There are in some institutions radioimmunoassays for prednisone and dexamethasone, but with the exception of the radioreceptor assay (discussed below) there is no test which detects all of these glucocorticosteroids. Since the exogenously administered steroids suppress the pituitary and hypothalamic stimuli to ACTH secretion, the plasma ACTH and plasma and urinary corticosteroid and ketosteroid levels are low. In today's case, the plasma cortisol as measured by the fluorimetric and corticosteroid-binding (CBG) isotope competition assays, the plasma ACTH, and the urinary hydroxycorticosteroid and ketosteroid levels were low. Dr. Philip Ballard, assistant professor of pediatrics, and I recently developed an assay for glucocorticoid activity which detects both natural and synthetic glucocorticoids.[7,8] The assay depends on the fact that steroids with glucocorticoid activity bind to the specific cytoplasmic glucocorticoid receptor (Chart 1) and thus can inhibit the binding of a radioactively labeled glucocorticoid. Further, the inhibition is proportional to the biologic potency and concentration of the competing steroids. Thus, a steroid such as dexamethasone would bind to these receptors more than cortisol even when present at, for example, only one-third the concentration of cortisol. The competition principle is similar to that utilized by the CBG-isotope competition technique now extensively used for measurement of plasma cortisol;[9] however, the cytoplasmic receptor is more specific for glucocorticoids than CBG (transcortin).[10] The principle is the same as that used in competitive radioimmunoassays and receptor assays developed for other hormones. For the assay, we use receptor from cultured rat hepatoma cells[10] for several reasons. This receptor has a very similar binding specificity as that of a human target tissue

TABLE 3.—*Diagnostic Tests in Iatrogenic Cushing's Syndrome**

Test	*Result May Be*	*Results in Present Case*
Plasma "cortisol"		
Fluorimetric	High or low	Low (2.7 μg/100 ml)
Porter-Silber	High or low	
CBG-Isotope competition	High or low	Low (2 μg/100 ml)
Glucocorticoid radioreceptor assay	High	High (30-40 μg cortisol equivalents/100 ml)
Urine		
17-Hydroxycorticoids	High or low	Low (0.6 mg/24 hours)
17-Ketosteroids	Low	Low (0.6 mg/24 hours)
"Free" cortisol	High or low	
Diurnal variation of plasma corticoids	Varies with dosage	Varied with dosage
Plasma ACTH	Low	Low (17 pg/100 ml)

*For review see reference 1. Assuming that ACTH administration is not responsible.

(lung)[9,10] with which it was compared. The only exception we have found after testing about 40 different steroids is that corticosterone (the predominant rat glucocorticoid) competes more effectively in our system than with the human receptor. Results of the assay are expressed as cortisol equivalents of glucocorticoid activity. For conditions associated with normal, low or high cortisol, the assay gives results similar to those obtained from the CBG-isotope competition[9] and fluorimetric assays. The principal advantage of the radioreceptor assay is that the synthetic glucocorticoids can also be measured.

The glucocorticoid activity in plasma from the patient presented today was measured by the radioreceptor assay. A rise in activity was found after her taking the "pink pill" (Chart 3); it was maximal at 90 minutes and then declined. In contrast, the cortisol levels determined by the CBG-isotope competition technique were low throughout the time period studied (Chart 3). Thus, the radioreceptor assay results supported our clinical impressions and in fact provided the only direct laboratory documentation that the patient was taking a glucocorticoid.

Note that the peak glucocorticoid levels were about 30 μg cortisol equivalent per 100 ml (Chart 3); since the upper limit of normal of plasma cortisol is only 25 μg per 100 ml, one might wonder how the patient could be severely Cushingoid at such levels. However, the biological activity of glucocorticoids in plasma is due to the free rather than the total corticoids.[2] Thus, an estimation of the free glucocorticoid activity would provide a better index of the true biological activity. The radioreceptor assay has been adapted to provide an approximation of free and total plasma glucocorticoids. This is possible since a

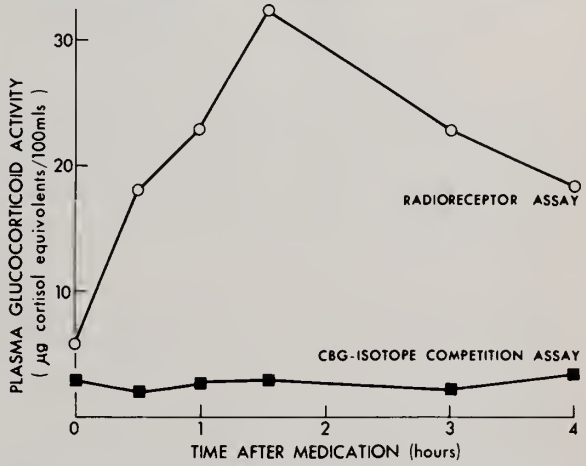


Chart 3.—Plasma glucocorticoid activity (expressed as μg cortisol equivalents per 100 ml plasma) following ingestion by the patient of the unknown medication ("pink pill") as determined by the radioreceptor assay (O—O).[7,8] Also shown, are cortisol determinations in the same plasma samples by the CBG-isotope competition assay (■—■).[6,9]

brief exposure of plasma to activated charcoal removes free and albumin-bound steroid, but transcortin-bound steroids remain in solution.[10]

Determinations of total and transcortin-bound cortisol by the radioreceptor assay agree well with results reported in the literature.[9,11] Chart 4 shows results from such determinations in the patient presented today. On the left is shown the normal range for plasma cortisol. In the center is shown the determinations in our patient's plasma after she had taken her prescribed dose of the "pink pill." Most of this glucocorticoid activity is not bound by transcortin, and thus the free glucocorticoid level is quite high.

The patient's medication was switched to 10 mg prednisone twice a day, and she noted in-

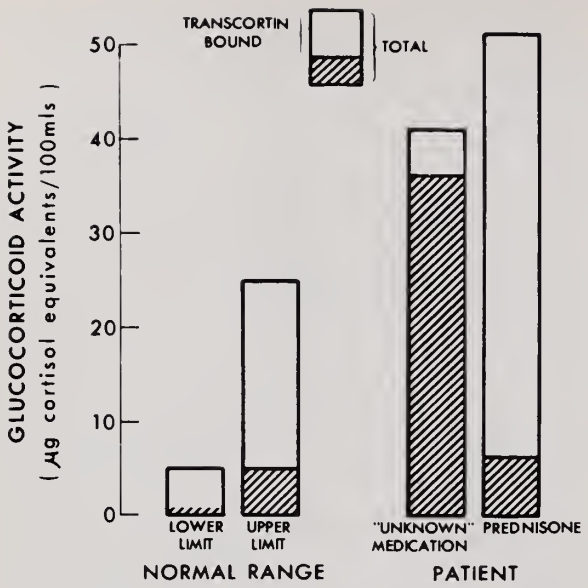


Chart 4.—Peak levels of total and transcortin-bound glucocorticoid activity (expressed by cortisol equivalents per 100 ml plasma) in the patient's plasma after taking the unknown medication (subsequently identified as triamcinolone) or 10 mg of prednisone. The range for normals is also shown.[11]

creased arthritic symptoms. Thus, it is likely that the prescribed dosage of prednisone was less potent than that of the "pink pill." This impression was confirmed by the radioreceptor assay (Chart 4). The total glucocorticoid levels in plasma were higher when she received prednisone than when she took the pink tablets, but the transcortin-free glucocorticoid activity was higher with the latter.

Usually the diagnosis of exogenous Cushing's syndrome is not difficult, since a history of glucocorticoid or ACTH intake is easily obtained. In the case presented this morning, glucocorticoid intake was strongly indicated, and yet a positive history could not be obtained. We were made particularly uncomfortable by the fact that her doctor and pharmacist in Mexico, who had resupplied her on several occasions with the pink tablets, repeatedly asserted that she was not receiving glucocorticoids. In this instance the radioreceptor assay results are quite helpful. Drs. Manfred E. Wolff and Robert Weinkam of the Department of Pharmaceutical Chemistry, subsequently analyzed the unknown medication by mass spectroscopy, ultraviolet absorption spectrometry and melting point determination and found that each tablet contained 1 mg of the potent glucocorticoid, triamcinolone.

Unfortunately, the case presented today is not an isolated incident of a patient receiving from Mexican sources pills not identified as glucocorticoids. We have been informed of a number of other similar cases. Undoubtedly other persons have received similar drug therapy but, along with their local physicians, were unaware of the nature of the medication and, therefore, the seriousness of continued therapy or abrupt withdrawal.

There is only one treatment for iatrogenic Cushing's syndrome and that is to slowly withdraw the drug. This is frequently difficult since symptoms of the primary disease may recur with decreased dosage and because the steroids have chronically suppressed the hypothalamic-pituitary-adrenal axis. Maintenance dosage must be given until one is certain of a well-functioning axis. Some of the symptoms that developed in our patient after abrupt withdrawal of the tablets she was taking could have been due to adrenal insufficiency.

REFERENCES

1. Christy NP: Iatrogenic Cushing's syndrome, *In* Christy NP (Ed): The Human Adrenal Cortex. New York, Harper and Row, 1971, pp 395-425

2. Baxter JD, Forsham PH: Tissue effects of glucocorticoids. Am J Med 53:573-589, Nov 1972

3. Feldman D, Funder JW, Edelman IS: Subcellular mechanisms in the action of adrenal steroids. Am J Med 53:545-560, Nov 1972

4. Munck A: Glucocorticoid inhibition of glucose uptake by peripheral tissues. Old and new evidence, molecular mechanism and physiological significance. Perspect Biol Med 14:265-289, 1971

5. Cahill GF: Action of adrenal cortical steroids on carbohydrate metabolism, *In* Christy NP (Ed): The Human Adrenal Cortex, New York, Harper and Row, 1971, pp 205-239

6. Cooke AR: The stomach and duodenum, *In* Sleisenger MH, Fordtran JS (Eds): Gastrointestinal Disease, Philadelphia, W B Saunders, 1973, pp 644-646

7. Ballard PL, Baxter JD: Measurement of natural and synthetic glucocorticoids: A new radioreceptor assay. Clin Res 22: 212A, Feb 1974

8. Ballard PL, Baxter JD: In preparation

9. Murphy BEP: Some studies of the protein-binding of steroids and their application to the routine micro and ultramicro measurement of various steroids in body fluids by competitive protein-binding radioassay. J Clin Endocr 27:973-990, Jul 1967

10. Rousseau GG, Baxter JD, Tomkins GM: Glucocorticoid receptors: Relations between steroid binding and biological effects. J Mol Biol 67:99-115, Jun 1972

Important Advances in Clinical Medicine

Epitomes of Progress—Psychiatry

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Psychiatry. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Psychiatry which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Psychiatry of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities
California Medical Association, 731 Market St., San Francisco, CA 94103

Depot Drugs and Chronic Schizophrenia

MOST CHRONIC SCHIZOPHRENIC PATIENTS require both maintenance antipsychotic medication and a comprehensive after-care system. The incidence of reappearance of overt psychotic symptoms is extremely high when neuroleptic medication is discontinued and frequently hospitalization is indicated for ambulatory patients. The exacerbation of psychotic symptoms is subjectively distressful and may be very disruptive to the patient, his family, and his social milieu. Depot neuroleptic drugs have made an important contribution to the physician's armamentarium, for they better allow for continued delivery of health care services to those schizophrenic patients who take their oral medication irregularly. Thus, long-acting injectable neuroleptics play an essential role in the effective and economical management of many chronic ambulatory schizophrenic patients.

Two phenothiazine-derivative depot neuroleptic agents are currently available in this country, fluphenazine enanthate (FE) and fluphenazine deconoate (FD), and are marketed under the trade names of Prolixin Enanthate®, and Prolixin Deconoate®, respectively. The basic pharmacologic effects of both are the same as for fluphenazine hydrochloride with the exception of duration of action.

Both FE and FD are highly potent agents and provide 25 mg per ml in a sesame oil vehicle parenterally. Local tolerance at the site of injection is good. The dosage range is from 0.25 ml to 3.0 ml per injection. The duration of action for FE is approximately two weeks with a range of one to six weeks. Extra pyramidal symptoms (EPS) are common with FE but are normally adequately controlled with an antiparkinsonism agent. In comparison, the duration of action may be increased and prevalence of EPS decreased for FD. For both FE and FD the onset of action generally appears one to three days following the injection, with a significant remission of symptoms within two to four days. Both can be given as a single agent for the treatment of the psychotic state without need for combination neuroleptic therapy. Most physicians prefer to substitute the depot agent for oral medication once the acute symptoms have subsided. Other clinicians, how-

ever, find it advantageous to directly administer the depot agent to some acutely psychotic patients, especially those who may be ambivalent about taking oral medication.

Patient rapport remains essential. Patients, including those on depot agents, frequently will not keep outpatient follow-up appointments if rapport is absent. Few schizophrenic patients will refuse to accept their physician's recommendation for depot neuroleptic drugs and follow-up appointments once a positive doctor-patient relationship has been established, thus also preserving the dignity of the patient to actively participate in his treatment program. Neuroleptic agents are best considered adjuncts to the overall longitudinal management and rehabilitative goals of the schizophrenic patient.

PATRICK T. DONLON, MD

REFERENCES

Chien C, Cole J: Depot phenothiazine treatment in acute phychosis: A sequential comparative clinical study. Am J Psychiatry 130:13-18, Jan 1973

Donlon P, Rada R, Knight S: A therapeutic aftercare setting for refractory chronic schizophrenic patients. Am J Psychiatry, In Press

Lithium in Pregnancy

LITHIUM CARBONATE is effective in the treatment of acute manic episodes in manic-depressive illness, and abbreviates acute depressive episodes in some patients with unipolar and bipolar depressions. Recent studies confirm that lithium also has prophylactic value: it reduces the frequency and intensity of recurrent manic and depressive attacks when it is administered indefinitely. Increasing numbers of women of childbearing age are being treated with lithium and the safety of the drug for mother and infant has become a matter of importance.

Teratology: The International Register of Lithium Babies, San Francisco, now contains reports of over 125 cases of fetal exposure to lithium. Analysis of these reports suggests a slightly higher than normal risk of fetal malformation in lithium-exposed pregnancies. A conservative position about lithium use in pregnancy thus seems warranted—a recommendation that pregnancy be avoided, stricter than usual criteria for use of lithium in women of child-bearing age, discontinuation of lithium during the first trimester if possible. Conception during lithium treatment does not appear, however, to be an indication for therapeutic abortion.

Maternal and Neonatal Toxicity: Because renal lithium clearance rises during pregnancy and falls at delivery, there is increased risk of lithium toxicity to mother and infant at the end of pregnancy. This risk can be minimized by: measuring maternal serum lithium weekly or more often in the last month of pregnancy, avoiding sodium-depletion via diuretics or salt restriction, and using the lowest dose of lithium sufficient to produce a maternal serum level in the effective range for prophylaxis (0.7 to 1.0 mEq per liter).

MORTON R. WEINSTEIN, MD

REFERENCES

Coppen A, Noguera R, Bailey J, et al: Prophylactic lithium in affective disorders—Controlled trial. Lancet 11:275-279, 1971

Schou M, Baastrup PC: Lithium prophylaxis in recurrent affective disorders. Br J Psychiatry 118:133-134, 1971

Goldfield MD, Weinstein MR: Lithium carbonate in obstetrics: Guidelines for clinical use. Am J Obstet Gynecol 116:15-22, 1973

The Peer Counseling Movement

PEER COUNSELING is loosely defined as psychological and social help given by non-professionals to persons of roughly their own age group. Currently, there is a surge in the youth peer counseling movement. Youth peer counselors often deal with crisis (for example, hotline) personal problems and situational stress but in addition have many programs that are primarily growth promoting. By growth they mean enhancing success, competence, and happiness in activities that are important to them, such as social, educational, play, sexual, and work activities.

In recent years the college youth in Davis, California, have developed diverse and extensive programs in the community and on campus which are models. There are now over 200 peer counselors in over 14 different agencies. For example, in the community, there is an adolesecent and youth center and an abortion counseling service and on campus a women's center, dormitory resident advisors, an academic advising center, and a general growth and counseling center. Campus services now command financial support from the university.

At the outset most peer counseling facilities focused on crisis and drug abuse-related problems. Now, the latter have become rare; rather they serve all kinds of mental health needs and problems, such as loneliness, interpersonal problems with family, friends or roommates, sexual problems, unwanted pregnancy, contraceptive advice, and depression. Many youths simply want to talk and relate with a friendly, accepting, listening, helping person. Youth today have a powerful urge to grow by mastering human communication

and this is accomplished by sharing meaningful thoughts and genuine feelings.

Programs include, not only one-to-one counseling, but many group activities. Personal exploration groups or encounter groups are popular and run throughout the year. There are workshops on various interests and skills including auto mechanics, Gestalt therapy, couples, life goals, meditation and yoga.

Peer counselors utilize some techniques developed by the professions of psychiatry and psychology such as listening, and in addition techniques developed by numerous other therapies such as bioenergetics, yoga, and massage. Counselors describe the helping process in terms of learning to share feelings, freedom to express feelings, forming a trusting relationship, enhancement of communication, identification, and sharing in a mutual growth process. Unlike professional psychotherapy, an essential ingredient of peer counseling is the mutual sharing of feelings, ideas, and outlook on life; a counselor talks honestly about himself. This results in reciprocal help. Counselors are careful to refer counselees to sources of professional help when indicated. There is no formal contract, no fees, no records are kept, and no appointments are necessary.

All counselors are volunteers. However, the counseling programs have their own structured training programs in which they utilize professionals. They maintain a stringent regular peer review system. As with psychotherapy, it is difficult to evaluate effectiveness but the professional services on campus have not encountered any casualties. Using rates of utilization of services as a yardstick of effectiveness, the peer counseling efforts at Davis are succeeding very well.

Peer counseling is a movement complementing professional work and doing things that professionals cannot do. In addition, they reach youth who can never be reached by the professional establishment. Physicians can assist peer counseling agencies by offering consultation, training and back-up care. A closer look at their activities will yield a wealth of information useful to the professional in his counseling and therapy.

GORDON D. JENSEN, MD

REFERENCES

Goodman G: Companionship Therapy. London, Jossey-Bass Inc, 1972

Hamburg BA, Varenhorst BV: Peer counselling in the secondary schools: A community mental health project for youth. Am J Orthopsychiatry 42:566-581, Jul 1972

Jensen GD, Maben M: Sex education and mental health work with a female teen-age gang. Hosp Community Psychiatry 24:151-155, Mar 1973

Indications and Contraindications for Minor Tranquilizers

A REVIEW of the last several years' literature on minor tranquilizers of which chlordiazepoxide (Librium®) and diazepam (Valium®) are the most common, reveals a large number of articles, letters and editorials which decry the use of tranquilizers as a type of panacea for the problems of living. Fortunately a recent paper by Parry and others brings the light of data into this area of philosophic disagreement. Parry and his coauthors found that use of tranquilizers in the United States is not greatly different from that of other Western European nations. In addition, about two-thirds of patients who utilized minor tranquilizers did so for a brief and intermittent period of time. Usage rates were found to vary widely, being higher among women, the middle-aged, and persons living in the West. During the period of time studied, one American in five had used a prescription psychotherapeutic drug of which the minor tranquilizers constituted about two-thirds. The highest proportion of long-term use among users was found among the least educated persons from the lowest socio-economic levels. No recent literature has seriously challenged the consistent finding that despite their wide popularity, positive placebo responses come within 5 to 10 percent of the favorable results achieved with minor tranquilizers. A few small studies have shown the superiority of exercise, meditation, or an evening glass of wine over the anxiety reducing effects of the minor tranquilizers.

The general indication for minor tranquilizers is for the symptomatic relief of anxiety, associated with functional states or illnesses. Therapy should be brief (two months or less), and if possible, intermittent, in order to allow the patient maximum opportunity to re-establish homeostasis. According to Parry, more than half of these situations will be directed to persons with a primary diagnosis of a physical, as opposed to a mental, disorder. It is doubtful that the patient with anxiety that persists for more than several months will, in general, be benefited by a continuation of a minor tranquilizer. Treatment-resistant patients may be benefited by brief counseling which explores the individual's adjustment in his family, work and leisure-time activities.

The only absolute contraindication is a known history of previous allergic response. Caution

should be utilized when sedation may be dangerous, such as operating machinery or an automobile. Another relative contraindication is anyone with a history of previous addictive problems since, despite efforts to find a non-addictive tranquilizer, all currently utilized compounds can be and are abused for their chronic and acute effects (high). It is not unusual for the alcoholic to become dependent upon a minor tranquilizer utilized in an effort to assist him in withdrawing from alcohol. Heroin addicts and other drug abusers make every effort possible to obtain large quantities of minor tranquilizers. The final relative contraindication is alluded to above in describing the nature of the symptomatic relief provided by these compounds. Since symptom relief only is obtained, minor tranquilizers should not be utilized on a chronic basis.

R. JAMES SPENSLEY, MD

REFERENCES

Denver HCB: Tranquilizers in psychiatry, chap 35.1, *In* Freedman AM, Kaplan HI (Eds): Comprehensive Textbook of Psychiatry. Baltimore, Williams and Wilkins, 1967, pp 1261-1262

Parry HJ, Balter MB, Mellinger GD, et al: National patterns of psychotherapeutic drug use. Arch Gen Psychiatry 28:769-783, Jun 1973

Psychotherapy of the Poor

THERE HAS BEEN increased consideration in psychiatry of the special needs of the poor. They, like all Americans, share in the dream of progress and affluence. Many poor people have not been appropriately treated in the past because psychotherapy evolved among upper middle class patients and was tailored to their needs. We now realize that the poor must have psychotherapy which is relevant to their particular needs. If we conceptualize all psychotherapy as being an educational experience, we see that we must start with poor patients and their life situations as they are.

Time is an important variable. One-sixth of all poor patients come only once for treatment and the average duration of therapy is six visits. We must therefore plan for brief, and at times, immediate problem solving.

All patients will reveal what they want the doctor to do. In addition to the typical middle class goals of increased awareness and self-understanding, poor patients present specific requests for aid in being emotionally supported, in regaining reality testing, control of oneself, coping with social institutions and so forth.

Treatment must take into account what it is the patient wants. This is a part of the marketing orientation in our culture wherein the patient is shopping and wants a particular service. He may not ask directly, so it is often necessary to look for what is being requested. Psychotherapy can proceed not only by providing the requested service, but secondarily by using our knowledge of human behavior to facilitate the patient's regaining emotional balance and ability to cope.

The techniques used are those by a physician as an involved, helping person, providing guidance or advice as needed. Methods used are reassurance, suggestion, ventilation and persuasion. The emphasis is on the present, on real problems as perceived by the patient. If the complaints are of symptoms, the treatment is to relieve them. For example, if the patient is anxious, a minor tranquilizer may be indicated, a phobic patient may need behavior therapy, and marital problems indicate conjoint therapy (husband and wife seen together).

All poor patients need a flexible approach specifically prescribed for their needs. They need to be confronted on their own grounds with an understanding of their wants, their social reality and present capacities. They must be treated not as we would want to be, but as they want to be. The physician should be a friendly, responsive and problem solving helper.

JOE YAMAMOTO, MD

REFERENCES

Yamamoto J: Optimal treatment for patients of all races and social classes in a Los Angeles clinic. Int Psychiatry Clin 8:143-166, 1971

Lazare A, Cohen F, Jacobson A, et al: The walk-in patient as a "customer": A key dimension in evaluation and treatment. Am J Orthopsychiatry 42:872-883, Oct 1972

Facial Expression of Emotion While Watching Television Violence

WHETHER EXPOSURE to violence on television leads to aggressive behavior or altruistic behavior can be predicted from facial expressions of emotion of male subjects. With five- and six-year-old boys those who look *happiest* while watching violence later aggressed more while those who looked *pained* and *disinterested* later helped more. This shows that for these young boys: (a) facial expressions while watching television reveal reliable information about emotion; (b) children differ markedly in their emotional reactions while watching violence on television; (c) these emotional reactions predict subsequent social behavior

including both aggressive and altruistic activities. Current research is investigating the psychological characteristics of children who tend to look happy while they view violence as compared to children who tend to look pained or disinterested when they see violence.

PAUL EKMAN, PH D
ROBERT LIEBERT, PH D
WALLACE V. FRIESEN, PH D

REFERENCES

Ekman P, Liebert RM, Friesen WV, et al: Facial expressions of emotion while watching televised violence as predictors of subsequent aggression, *In* Comstock GA, Rubinstein EA, Murray JP (Eds): Television and Social Behavior, Vol. V—Television's effects: Further explorations. Technical report to Surgeon General's Scientific Advisory Committee on Television and Social Behavior, Washington, U.S. Government Printing Office, 1972, pp 22-58

Ekman P, Friesen WV, Ellsworth P: Emotion in the Human Face: Guidelines for Research and an Integration of Findings. New York, Pergamon Press, 1972

Emergency Treatment of Mania

MANIC REACTIONS OCCUR both as primary disorders, in the manic phases of recurrent manic-depressive illness, and as accompaniments of thought disorders, as in schizoaffective schizophrenia. Manic symptoms include rapidity of thought process (itself often resulting in some disorganization of thinking), pressure of speech, expansive but mercurial mood, and excess motor activity. Frank manic episodes are less frequent than the so-called "hypomanic" states. However, the behavioral overactivity of both may be threatening to others as well as causing great physical strain on the individual himself. This is especially so if the patient has an already compromised physical status, such as having cardiovascular disease.

Although much remains to be learned about the etiology of manic reactions, it appears that the neurochemical substrate is an imbalance of biogenic amine neurotransmitters (norepinephrine, dopamine, serotonin), and perhaps other neurotransmitters, in the brain stem and limbic system. Compounds which increase the functional levels of amine neurotransmitters generally have antidepressant effects, and conversely, those which reduce neurotransmitter activity have antimanic effects. These latter drugs include the phenothiazines, butyrophenones, and lithium. All are useful in treating the acute manic episode.

The most rapid pharmacologic treatment of acute mania is with parenteral anti-psychotic agents. For most cases, a single sedative phenothiazine such as chlorpromazine will suffice. For severe cases, chlorpromazine 25 mg and trifluoperazine 2 mg may be given together parenterally in repeated doses. Oral administration may be used if the patient is sufficiently cooperative. In recent years lithium carbonate has been recognized as an effective antimanic agent, both to treat the acute episode and prophylactically to prevent recurrences. Lithium has a relatively low margin of safety, however, and blood levels must be monitored carefully. Its effects are not manifest for several days, and the dosage must be reduced when the manic episode begins to resolve.

Hospitalization to protect the patient and to facilitate effective treatment is usually indicated. If the acute manic episode is so severe as to be an extreme medical emergency, several electroconvulsive treatments in the same day may be used for immediate control.

ROBERT T. RUBIN, MD

REFERENCES

Cohen RA: Manic-depressive reactions. Comprehensive Textbook of Psychiatry. Baltimore, Williams and Wilkins, 1967, pp 676-688

Freyhan FA (Ed): Lithium: Clinical and biological aspects. Int Pharmacopsychiatry 5:77-264, 1970

Biofeedback in the Treatment of Chronic Anxiety

CHRONIC ANXIETY is a painful and, at times incapacitating condition, which affects approximately 5 percent of the United States population. Studies have shown that chronically anxious patients tend to be over-aroused—for example, they have increased activity of the sympathetic nervous system and tense muscles, even at rest. A number of treatment regimens designed to teach anxious patients to substitute muscular relaxation for their habitual over-vigilant posture have been reported to diminish chronic anxiety. Modern electronic technology allows patients to learn muscular relaxation more rapidly and efficiently by using biofeedback techniques. In addition, biofeedback technology facilitates the learning of profound frontalis muscle relaxation. This muscle is extremely difficult to relax voluntarily and its relaxation appears to correlate with decreased cortical arousal.

Ten chronically anxious patients, who had remained symptomatic despite two years of psychotherapy and numerous medication trials, were taught frontalis muscle relaxation by use of biofeedback techniques. All learned to maintain profound frontalis muscle relaxation for 25 minutes with or without feedback. One patient incorpo-

rated relaxation into his daily activities and experienced a dramatic decrease in his pervasive anxiety. Three patients used relaxation to control previously intolerable situational anxiety. Six of the anxious patients had severe insomnia. Five of them learned to relax themselves to sleep, but often awoke during the night. However, they could relax back to sleep and were no longer reliant on the sedatives they had used for years. Four of the patients who had accompanying tension headaches reported pronounced improvement in this symptom.

Currently, other biofeedback techniques are being explored for their possible effectiveness in alleviating chronic anxiety. For example, patients are being trained to control both muscle tension and heart rate. Moreover, feedback-induced muscle relaxation has allowed patients, who had previously been too anxious to relax, to benefit from desensitization procedures.

MARJORIE RASKIN, MD

REFERENCES

Raskin M, Johnson G, Rondesvtedt JW: Chronic anxiety treated by feedback-induced muscle relaxation. Arch Gen Psychiatry 28:263-267, Feb 1973

Stoyva J, Budzynski T: Cultivated low arousal—An anti-stress response, *In* DiCara LV (Ed): Recent Advances in Limbic and Autonomic Research, New York City, Plenum, 1973

The Dying Child

RECENT STUDIES have shown that the child over four or five years of age who has a terminal illness does realize its seriousness and probably fatal outcome even when told otherwise. The maturity of a child's concept of death is related to his emotional and cognitive stage of development. Although the younger child may have an immature concept of death, the very thought is often associated with anxiety. Such children tend to think of death in terms of aggression or of separation or a combination of the two, either of which may be a source of anxiety. In supportive care of the dying child, honesty and truthfulness are important from those who work with him. Communication should be open so that the child feels free to voice his feelings of sadness, fear, helplessness, loss and anxiety. Parents and professionals must maintain the patient in realistic hope through conveying to the child that he will not be isolated physically or emotionally, that those upon whom he depends will not desert him, that there will be relief from pain, and that there is excellence in medical care.

Those involved in care of the dying child are inevitably involved in care of the dying child's family during the course of the illness and afterward. Each family member's reaction to terminal illness and subsequent loss is not only intrapsychic but inevitably interrelated with altered family dynamics. Each experiences a profound crisis with persisting effects which all too frequently are pathological. In a report of a retrospective study within a pediatric hematology clinic of 20 families who had lost a child from acute leukemia, it was found that in half the families studied, one or more members ultimately required psychiatric care. Also, in more than half, one or more previously (seemingly) well-adjusted siblings showed altered behavior patterns that indicated considerable difficulty in coping. Although these symptoms generally became manifest during the course of the sibling's terminal illness, the more severe reactions followed the actual death of the sibling and persisted.

The implications of this for preventive mental health are significant. One cannot focus on care of the dying child without considering the entire family.

Such families often need support from professionals in coping with the emotional impact of a child who is dying so that they in turn can provide the necessary support to the dying child. Subsequently, during the trying months after the death, many families need help in carrying out grief work.

CHARLES M. BINGER, MD

REFERENCES

Binger CM, Ablin AR, Feurstein RC, et al: Childhood leukemia: Emotional impact on patient and family. N Engl J Med 280:414-416, Feb 20, 1969

Anthony EJ, Koupernik C (Eds): The Child in His Family: The Impact of Disease and Death, *In* Yearbook of the International Association of Child Psychiatrists and Allied Professions, Vol 2, New York, Wiley Interscience, 1973

Homicide Prevention

INJURIES DUE to physical assaults are increasing, and, despite improvements in the availability and effectiveness of emergency room medicine, deaths from homicide also are increasing. The California homicide rate rose from 4.5 per 100,000 population in 1960 to 7.6 in 1970. A majority of murders are committed by friends or relatives of the victim. One-fourth of all murders occur within the family.

Workers in emergency telephone counseling and crisis intervention services report that 5 to 10

percent of calls involve threats of homicide as well as suicide. Homicidal behavior resembles suicidal behavior in three aspects: crisis, ambivalence and an appeal or demand for change enforced by a threat of violence. The danger of homicide is highest when the individual is angry, abusing alcohol, has a weapon and feels hopeless about life.

Often, physicians can help restore communication in a family, and provide a forum for an inarticulate frustrated spouse. Potential victims of homicide may be encouraged to get guns and other weapons out of the house, seek help or sometimes leave the scene. When children are at risk, the physician has a moral and legal responsibility. Often, patients on the verge of committing homicide are suffering from a severe, unadmitted, depressive reaction which is amenable to treatment.

ROBERT E. LITMAN, MD

REFERENCES

Kozol AJ, Boucher RJ, Garfalo RF: The diagnosis and treatment of dangerousness. Crime and Delinquency, 371-392, Oct 1972

MacDonald JM: Homicidal Threats. Springfield, Ill., Charles C Thomas, 1968

Parents of Battered Children

PRESENT-DAY CLINICAL AND RESEARCH FINDINGS view the genesis of child maltreatment as rooted in the impoverishment or absence of adequate "mothering" during the formative months and years of the abusing parent's life. This impoverishment in turn leads to failure in the development of trust, which then results in interpersonal isolation, and withdrawal from later adult relationships of intimacy and sharing. Recognizing the impact of this deficiency of parenting in abusing and maltreating mothers and fathers, multi-disciplinary teams responded with multi-dimensional techniques for intervention and prevention.

Today traditional programs of individual and group psychotherapy are augmented by enrollment of parents and children in therapeutic day-care centers, and by use of specially selected and trained volunteers, who, available the clock around to specified families, become parent surrogates for the troubled and overwhelmed parents of abused children. In addition, self-help groups such as Parents Anonymous, and regularly scheduled, but informal, classes on parenting and child care, concurrent with other therapeutic and community-based outreach programs are proving most helpful. These approaches are the foundation for multi-dimensional programs whose goals are intervention, education, and prevention of child abuse. Such multi-therapeutic approaches can today contribute significantly to the successful rehabilitation of 90 percent of those mothers and fathers identified as having a child "at risk."

MORRIS PAULSON, PH D

REFERENCES

Helfer RE, Kempe CH: The Battered Child. Chicago, The University of Chicago Press, 1968

Second National Symposium on Child Abuse: The American Humane Association, Children's Division, Denver, 1973

ADVISORY PANEL TO THE SECTION ON PSYCHIATRY

JOHN S. PECK, MD, *Chairman, Encino*
Chairman, CMA Section on Psychiatry

HARVEY SMALL, MD
CMA Section on Psychiatry, Secretary
San Mateo

GEORGE A. GROSS, MD
CMA Section on Psychiatry,
Assistant Secretary
CMA Scientific Board
Sacramento

THOMAS A. GONDA, MD
CMA Scientific Board
Stanford

M. ROBERT HARRIS, MD
CMA Scientific Board
San Francisco

HERBERT E. VANDERVOORT, MD
CMA Scientific Board
San Francisco

NORMAN I. GRAFF, MD
San Mateo

HARRISON S. EVANS, MD
Loma Linda University

DAVID A. HAMBURG, MD
Stanford University

DONALD G. LANGSLEY, MD
University of California, Davis

LOUIS A. GOTTSCHALK, MD
University of California, Irvine
California College of Medicine

LOUIS J. WEST, MD
University of California, Los Angeles

ARNOLD J. MANDELL, MD
University of California, San Diego

ALEXANDER SIMON, MD
University of California,
San Francisco

EMMANUEL SILVER, MD
Palo Alto

JOHN ECKS, MD
Coronado

HAROLD MANN, MD
Berkeley

SIGMUND GABE, MD
Beverly Hills

DONALD H. NAFTULIN, MD
Los Angeles

MELVIN M. LIPSETT, MD
Berkeley

LLOYD C. PATTERSON, MD
Berkeley

WILLIAM MEYER, MD
Sacramento

R. BRUCE SLOANE, MD
University of Southern California
Los Angeles

EDITORIAL

More on PSRO's

TWO THOUGHTFUL PAPERS on the pros and cons of the Professional Standards Review Organizations (PSRO's) appear elsewhere in this issue. The authors of both are noted for the depth of their perception and of their scholarship in the problems of assuring the quality of medical care in today's political and practice environment. At the present moment there is no general agreement about how best to deal either with the PSRO's mandated by Public Law 92-603 or how else to provide the necessary public accountability for the quality and appropriateness of patient care paid for with some 31 billion of the taxpayers' dollars. So far the heat generated has been fairly intense. It is hoped that the papers of Sanazaro and White will provide some new and needed illumination for professional examination of this perplexing problem which is unlikely either to be consumed by the heat it generates or otherwise to disappear.

—MSMW

Legg-Calvé-Perthes

Legg-Calvé-Perthes disease has been comprehensively reviewed elsewhere in this issue of THE WESTERN JOURNAL OF MEDICINE.

Recently Michael A. R. Freeman of London[1] demonstrated the model of this disease by creation of successive "infarcts" of the femoral head in dogs, weakening the supporting structures of the proximal femoral epiphysis. Again Legg-Calvé-Perthes disease is simulated in the laboratory and is attributed to a vascular insufficiency but its true etiological mechanism in the child eludes us.

An "irritable" hip joint in the limping child is suspect. The "irritable" hip as evidenced by limited motion should be of major concern to the treating physician. To accept the concept that "there is no difference in the long term results of the treated or untreated care of Legg-Perthes" is to condemn a certain number of children to an avoidable hip problem at skeletal maturity.

In the last ten years there has been a revival of interest in this condition. Though the cause is elusive, knowledge of the disease has increased and its treatment improved. Containment of the femoral head in the acetabulum has in the past given, and will continue to give, good prognosis for recovery. The more conservative approach of traction can be followed until there is a full range of motion without irritability. Closed or open surgical procedure with release of a tight iliopsoas or adductors of the hip to achieve containment and maintained in the acetabulum until the disease is well into the reparative phase will give a satisfactory result. The containment, whether by conservative traction or open reduction, can be maintained by abduction casts as described by Petrie with combined abduction of 90 degrees and internal rotation as tolerated. Weight-bearing is preferable in the casts to help hold the mold of the head in the acetabulum. Over the past five years we have not found it necessary or advisable to perform osteotomy of either the acetabulum or femoral side of the joint to achieve "containment" in the degenerative phase of the disease. Some surgeons continue to advocate these latter procedures to contain the femoral head that has escaped the periphery of the acetabulum.

Our recent series of approximately twenty patients treated consecutively during the past eight years, with 90 degrees of combined abduction maintained, has borne out the important additional dividend described by Petrie. In no patient has the hip that was uninvolved at the time of initial treatment been subsequently involved with Legg-Calvé-Perthes disease.

There is abundant and growing evidence that Legg-Calvé-Perthes disease does indeed warrant continued treatment from onset of symptoms until well into the reparative phase.

G. WILBUR WESTIN, MD
Chief Surgeon
Shriners Hospitals for Crippled Children
Los Angeles Unit

REFERENCE

1. Freeman MAR: Address given to American Academy of Orthopedic Surgeons, Dallas, Texas, Jan 1974

Biological Uniqueness and the Quality of Life

RECENT ADVANCES in biological science, particularly in the field known as molecular biology, have demonstrated beyond any doubt the biochemical and therefore the biological uniqueness of every person. Each human life starts with a unique set of genes whose chemical structure determines the physical, mental and emotional endowment of the person. And then, from the moment of conception and until death, the environmental experience which is also unique for each person reacts with this body chemistry to influence, modify and change it. Thus every person, even each of genetically identical twins, is biochemically and biologically unique with unique needs for personal fulfillment to give quality to his or her life.

So far, biological science has provided little hard data to explain the origin of life and even less upon its value or purpose. Nor does biological science say anything about the meaning or implication of biological uniqueness in terms of the human potential for personal fulfillment or the quality of the life which is to be led. It is here that biological science merges into medicine and medicine merges into the art and science of living within biological law and the physical and cultural framework of the world biosphere and of modern human society.

What are the implications of this for medicine? First it suggests a core tenet for medicine. Not only practicing physicians but the profession as a whole should give greater recognition to the importance of the fundamental uniqueness of each person, and all that this in turn implies for patient care and indeed for social, economic, political and even legislative action by the profession. And second it suggests that personal fulfillment and the quality of life will also be different and unique for each person, and that this will be what is attainable within his or her physical, emotional and situational capabilities and limitations. In terms of human society and the world biosphere, personal fulfillment must of course be tempered by the rights and needs of others for the same, and by the need to create and preserve an environment which will support the quality of life which is desired.

The particular professional expertise of medicine lies in illness and health. However, these are not to be separated from the reality of biological individuality, the goal of personal fulfillment, the quality of life, and the environmental situation which all pertain uniquely to every human being. They are each part and parcel of the diagnosis and treatment of illness and of the restoration and maintenance of health. The implications of this for the practice of medicine are enormous and extend far beyond patient care and into the role of medicine in the social, economic, political and legislative framework of the world biosphere and modern society. This has yet to be explored.

It is suggested that there is great potential for prestige and power in this for modern medicine in modern society. A posture of strong advocacy of the fact of biological uniqueness of every person which links the goal of personal fulfillment and the quality of life to health, illness, and social, economic and political progress, would surely be worthy of our profession. If properly developed and properly applied, such a posture could become a tremendous force for "the betterment of the public health" in our evolving society.

—MSMW

Treatment of Ventricular Septal Defect

IN THE SPECIALTY CONFERENCE which appears elsewhere in this issue of THE WESTERN JOURNAL OF MEDICINE, Dr. Friedman discusses thoroughly a common, major congenital heart lesion—the large ventricular septal defect causing congestive heart failure and retarded growth. Because of the importance of the subject some added emphasis and qualifications are set down here.

The isotope dilution technique described is not in general use. It is semi-quantitative at best, not able to detect very small shunts, does not define the site of the defect and, being empirical, is subject to errors due to unknown variables. It may be replaced by the more soundly based gamma function analysis recently described and is better used for screening and follow-up than for diagnosis.

The data of Charts 1 and 2 in the Specialty

Conference might be clearer if the natural histories of small, moderate and large defects are separated.

Small defects (murmur, no or minimal cardiomegaly, normal pulmonary arterial pressures, pulmonary blood flows under twice systemic flows) are asymptomatic and they make up 65 to 75 percent of all ventricular septal defects at birth. They do not cause heart failure or pulmonary vascular disease, and the major complication associated with them—bacterial endocarditis—is probably uncommon. About 50 to 75 percent of them close spontaneously by 15 years of age, and Dr. Friedman emphasizes correctly that the risk of treating small defects conservatively is less than the risk of surgical complications of defect closure.

Moderate defects (moderate cardiomegaly, pulmonic flow two to three times systemic flow, pulmonary arterial pressure under 50 percent of systemic pressure) usually cause moderate congestive heart failure that responds well to medical treatment. These defects account for 20 to 25 percent of ventricular septal defects at birth. They tend to close or get smaller spontaneously, usually under three years of age but sometimes after many decades. If they remain moderate sized, pulmonary vascular disease may develop after 15 years of age, as may occur in physiologically similar atrial septal defects. Therefore we recommend surgical closure at about five years of age when there are big shunts and big hearts or symptoms. Smaller defects in this group can be treated conservatively.

The large defects account for 10 to 15 percent of ventricular septal defects at birth. As Dr. Friedman mentioned, the left-to-right shunt increases as the high fetal pulmonary vascular resistance falls after birth. In term infants the increasing left ventricular volume load usually causes overt congestive heart failure between six weeks and six months of age, but in preterm infants, with a lower pulmonary vascular resistance at birth, heart failure with a big defect usually presents before two months of age. At any age, overt congestive heart failure is usually preceded by irritability, excessive sweating, poor weight gain and tachypnea.

Rarely, when heart failure is intractable, early operation is needed. In many centers, surgical closure of the defect has replaced pulmonary artery banding. Banding is often imperfect, has a 6 to 10 percent mortality rate, has complications (for example, obstruction of one pulmonary artery, thickening of the pulmonary valve) and increases the duration and mortality of subsequent corrective surgery. If a surgical team can close defects in infants with a mortality rate of less than 10 percent, banding should be restricted to unusual problems such as multiple muscular defects and associated complicating lesions.

If congestive heart failure is partly controlled but growth is poor, many cardiologists would disagree with Dr. Friedman that early operation is warranted, especially if this means an extra operation (banding) or the higher risk of closing the defect in a tiny infant. Our group would defer operation to allow the child to grow and improvement to come about spontaneously. Spontaneous closure occurs in 5 to 10 percent of the large defects and as many as 50 percent of them may get small enough to eliminate concern. If the defect remains large, however, then the risk of obliterative pulmonary vascular disease is high. Both a smaller defect and pulmonary vascular disease will decrease the shunt and cause subjective and objective improvement.

Unfortunately, cardiac catheterization is the only certain way of determining if pulmonary vascular disease is beginning. The pulmonic component of the second heart sound is loud in large ventricular septal defects whether resistance is high or low, and by the time the smaller heart as observed on x-ray films and pure right ventricular hypertrophy as observed by electrocardiogram indicate pronounced pulmonary vascular disease, it may be irreversible. Therefore the safest way of handling these infants is to do cardiac catheterization studies when they present with heart failure (to define anatomy and physiology) and then repeat such studies six to nine months later to determine changes in defect size and pulmonary vascular resistance. If a rising resistance is found, it is usually reversible after closure of the defect, an operation that can be safely undertaken at this age. Research into non-invasive methods of measuring pulmonary blood flow may allow better timing of recatheterization in future, but even at present in experienced laboratories cardiac catheterization is safe enough to be used, more than once if necessary, to select the appropriate patient and time for corrective operation.

JULIEN I. E. HOFFMAN, MD
Department of Pediatrics, and Cardiovascular Institute
University of California, San Francisco

CASE REPORTS

Refer to: Tuxen P, Buscaglia L: Hepatic artery injury in nonpenetrating trauma. West J Med 120:317-318, Apr 1974

Hepatic Artery Injury in Non-Penetrating Trauma

PETER TUXEN, MD
LUCIAN BUSCAGLIA, MD
Stockton, California

NOT OFTEN does blunt trauma cause injury to any visceral artery,[1] and isolated damage to the hepatic artery from blunt trauma is therefore a rarity. Such an injury occurred in the following case.

Report of a Case

A 16-year-old boy was involved in a single car crash and was not wearing a seat belt. On admission to hospital he did not appear acutely ill but he complained of pain in the right upper quadrant of the abdomen. Blood pressure was 110/60 mm of mercury and pulse rate 112. An abrasion over the left lower rib cage and tenderness in the central abdomen were the only physical findings. An x-ray film showed left-sided rib fractures, six through ten.

The hematocrit was 43 percent and leukocytes numbered 29,000 per cu mm. Paracentesis yielded bloody fluid. An upper midline incision was made in the abdomen and 500 ml of clotted blood was found in the peritoneal cavity. A hematoma was present in the region of the lesser sac and the hepatoduodenal ligament, and manipulation induced fresh arterial bleeding. The portal triad was carefully explored and a tear in the superior medial aspect of the proper hepatic artery was noted and repaired. The next morning a selective celiac artery arteriogram showed complete obstruction of the hepatic artery distal to the origin of the gastroduodenal artery (Figure 1). At this time the blood pressure and pulse were within normal limits and the patient appeared generally well. Results of laboratory tests were within normal limits except for leukocytosis and elevated serum transaminase.

At re-operation, multiple patchy areas of infarction were evident in right and left lobes of the liver. Circumferential mobilization of the common hepatic and proper hepatic artery was carried out. A localized thrombosed segment was resected and the vessel was reconstructed by an interposition saphenous vein graft. The distal anastomosis was facilitated by placement of an inlying no. 10 silastic catheter and the junction was made with interrupted 6-0 cardiovascular suture.

Postoperative recovery was rapid and uncomplicated except for a few days of low grade fever. The patient was discharged home on the ninth postoperative day. Liver function tests showed return toward normal levels (Chart 1) and at four months after the operation the patient appeared entirely well. Arteriograms showed no improvement from the earlier intraoperative study (Figure 2).

Discussion

In a major review of the subject of hepatic trauma, Madding and Kennedy[2] found reports of 23 cases of common or branch hepatic artery injury following blunt trauma. Ligation was used in the management of complicated liver injuries. In a case comparable to the one reported here, Bushkin and coworkers recently described hepatic artery dissection from nonpenetrating trauma to the celiac axis.[3]

In the present case, a tear in the hepatic artery was recognized at emergency laparotomy, and an attempt at simple repair was unsuccessful. Cyanosis with patchy infarction was observed at reoperation, and reconstruction of the artery was again attempted and was again unsuccessful. Nevertheless, liver function improved and the patient did well. Had arteriography not been repeated the repair would have been assumed to have been successful.

From Department of Surgery, San Joaquin General Hospital, French Camp, California.

Submitted, revised, September 10, 1973.

Reprint requests to: L. Buscaglia, MD, 2420 N. California Street, Suite 21, Stockton, CA 95204.

Figure 1.—Celiac arteriogram after the initial laparotomy. A metal clip overlies obstruction near point at which tear in hepatic artery was oversewn. Presumably, the repair compromised the vessel lumen, allowing thrombosis to ocur. Retrograde filling of the hepatic artery distal to the obstruction indicates that collateral flow is already present. (SA = splenic artery; CHA = common hepatic artery; GDA = gastroduodenal artery; LGA = left gastric artery; PHA = proper hepatic artery.)

Figure 2.—Arteriogram six weeks after attempted saphenous vein interposition still showed no direct hepatic artery flow.

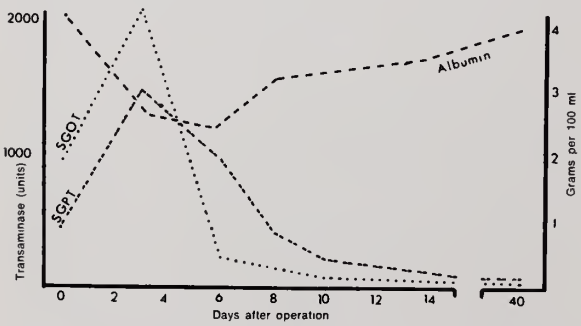


Chart 1.—Graph represents serial serum levels of glutamic oxalic and pyruvic transaminase after proper hepatic artery injury and permanent interruption. Bilirubin and alkaline phosphatase remained about normal at all times.

Such a favorable outcome is consistent with the current concept that hepatic artery ligation is well tolerated.[2,4,5] Ligation has been performed, with satisfactory results, for arteriovenous fistula, malignant disease, cirrhosis with ascites, aneurysm and hemobilia. A normal liver can probably tolerate dearterialization, but there is a significant difference between common and proper hepatic artery ligation. The former produces no ischemic changes, presumably due to collateral flow via the gastroduodenal artery. On the other hand, proper hepatic artery ligation causes necrosis and temporary liver function impairment.[2] Because proper hepatic artery occlusion may represent a potentially fatal lesion, we believe repair is indicated. However, the liver's metabolic needs for survival and regeneration are met by increased extraction of portal vein oxygen.[6] The existence of small arterial collaterals to the liver is well documented,[7] but most investigators believe this is a less important factor. Nevertheless, in the present case collateral flow around the site of proper hepatic artery ligation was shown in the early postoperative period. This may have accounted for the minimal morbidity and prompt recovery.

Postoperatively, maintenance of normal blood volume and the avoidance of hypoxemia are important to support a developing collateral circulation. Because of associated injuries, antibiotics may be necessary but would not be indicated for prophylaxis at the operative site alone, even in the face of hepatic infarction, since portal venous blood is sterile.

Summary

A previously unreported complication of blunt abdominal trauma, laceration of the proper hepatic artery, is reported. Because this may be a potentially fatal lesion, repair is indicated. Factors influencing survival relate to pre-morbid status of liver, preservation of splanchnic venous flow, and support of collateral circulation.

REFERENCES

1. Buscaglia LC, Lim R, Blaisdell FW: Penetrating abdominal vascular injuries. Arch Surg 99:764-769, Dec 1969
2. Madding GF, Kennedy PA: Hepatic artery ligation. Surg Clin North Am 52:719-728, Jun 1972
3. Bushkin FL, MacGregor MC, Hawkins IF, et al: Hepatic artery dissection as a result of abdominal trauma. Surg Gynecol Obstet 135:721-726, Nov 1972
4. Mays ET: Observation and management after hepatic artery ligation. Surg Gynecol Obstet 124:801-807, Apr 1967
5. Kim DK, Kinne DW, Fortner JG: Occlusion of the hepatic artery in man. Surg Gynecol Obstet 136:966-968, Jun 1973
6. Tygestrup N, Winkler K, Mellemgaard K, et al: Determination of hepatic artery blood flow and oxygen supply in man by clamping the hepatic artery during surgery. Clin Invest 41:447. 1962
7. Bengmark S, Rosengren K: Angiographic study of the collateral circulation to the liver after ligation of the hepatic artery in man. Am Surg 119:620-624, Jun 1970

Refer to: Coskey RL, Danzig R: Cardiac arrest due to extreme tachycardia with Wolff-Parkinson-White syndrome. West J Med 120:319-321, Apr 1974

Cardiac Arrest Due to Extreme Tachycardia with Wolff-Parkinson-White Syndrome

RICHARD L. COSKEY, MD
RONALD DANZIG, MD
Sherman Oaks, California

A 17-YEAR-OLD HIGH SCHOOL STUDENT with a five-year history of paroxysmal tachycardia was admitted to hospital on 2 November 1971. Previous episodes had varied in length from 10 to 70 minutes, were precipitated by exertion or excitement and were associated with weakness, soreness of the back and diaphoresis, without polyuria or dyspnea. The patient participated in normal high school physical education. Results of a system review were negative except for symptoms associated with episodes of recurrent tachycardia. The father was said to have hypertension and diabetes mellitus. There was nothing to suggest a family history of Marfan's syndrome. Before admission to hospital the patient had been jogging when he noted sudden onset of tachyarrhythmia. He was immediately brought to the emergency room where functional cardiac arrest occurred, as shown by loss of consciousness and inability to obtain blood pressure during the recording of the electrocardiogram (Figure 1). He responded successfully to immediate direct current (DC) cardioversion.

On physical examination following cardioversion the patient was tall and thin. He appeared to be in no distress. Height was 72½ inches with arm span of 74½ inches. The fingers and toes

Submitted July 19, 1973.

Reprint requests to: R. L. Coskey, MD, Cardiology Consultants Medical Group, Inc., 4911 Van Nuys Blvd., Sherman Oaks, CA 91403.

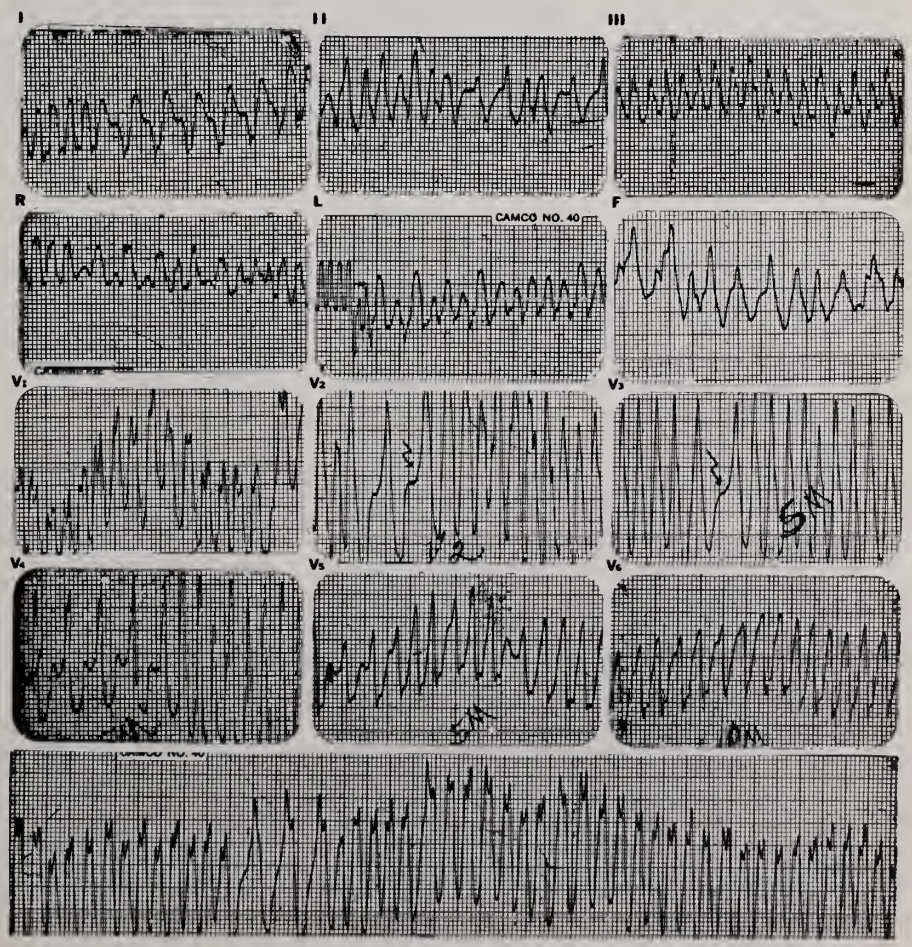


Figure 1.—Electrocardiogram recorded during tachyarrhythmia, showing atrial fibrillation with aberrant ventricular conduction.

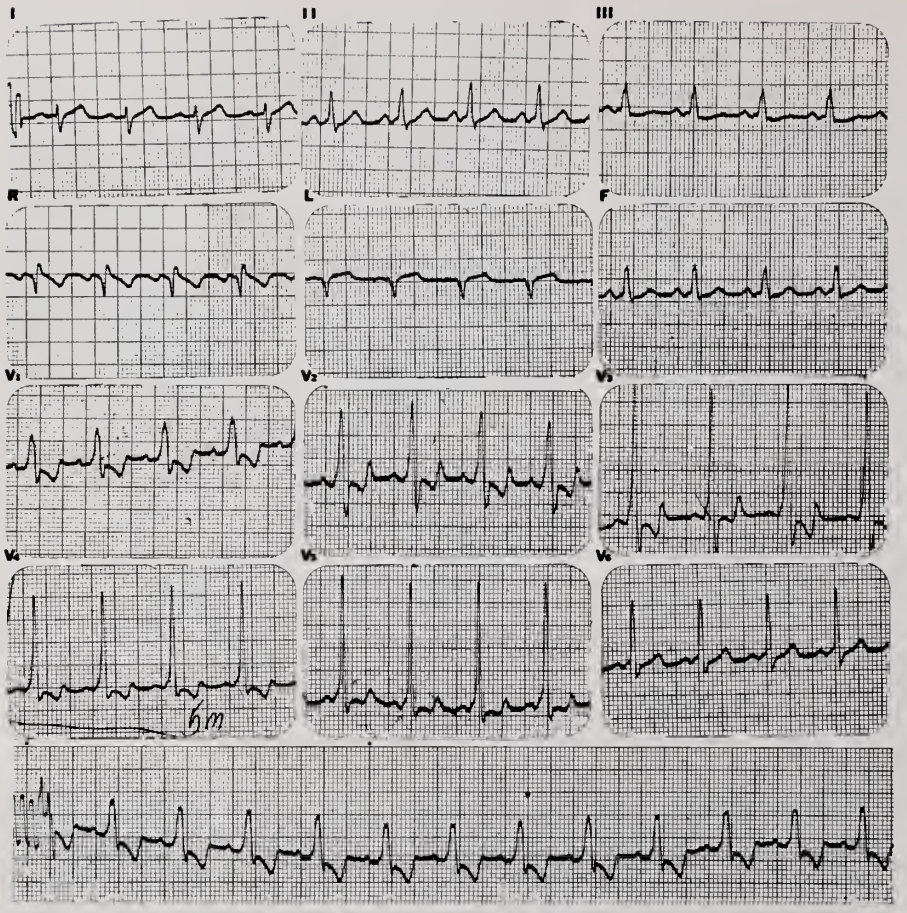


Figure 2.—Electrocardiogram recorded one and a half hours after direct current cardioversion of tachyarrhythmia, revealing type A Wolff-Parkinson-White syndrome with primary ST-T abnormalities.

were long and thin. There were no ocular, cardiac or musculoskeletal abnormalities to suggest Marfan's syndrome or other connective tissue disorder. Cardiac pulsations were normal, as were first and second heart sounds. No murmur or abnormal sounds were noted. Results of chest x-ray studies were within normal limits.

Propranolol was administered in a dosage of 10 mg four times daily and later reduced to 30 mg per day. There were two recurrences of tachyarrhythmia lasting 10 minutes. They were not associated with loss of consciousness and cleared spontaneously. Propranolol was increased to 20 mg four times daily and there were no further recurrences of tachycardia. The electrocardiogram recorded on 2 November during the functional cardiac arrest showed atrial fibrillation with a very rapid slightly irregular ventricular rhythm averaging 338 beats per minute and varying from 215 to 400 beats per minute. The QRS duration was 0.10 seconds. The RR interval was as short as 130 milliseconds (Figure 1). The post-conversion electrocardiogram was consistent with type A Wolff-Parkinson-White (W-P-W) syndrome (Figure 2). Subsequent electrocardiograms demonstrated reversion of the ST-T abnormalities to normal and persistent frontal plane QRS axis of +100° (Figure 3). During the tachyarrhythmia the mean QRS vector was directed to the right, inferiorly and anteriorly with the T wave vector directed to the left, superiorly and posteriorly.

Discussion

The extremely rapid and slightly irregular ventricular response averaging 338 beats per minute and at times approaching 400 beats per minute is even more rapid than the ventricular rate reported with atrial flutter with 1-1 conduction.[1]

The possibility of ventricular tachycardia cannot be completely ruled out, but as has been pointed out by others,[2] the widening of the QRS complexes in tachycardia associated with the W-P-W syndrome usually represents aberrant ventricular conduction simulating ventricular tachycardia. RR intervals averaging 178 milliseconds and as short as 124 milliseconds are significantly less than the average basal atrioventricular (AV) conduction system functional refractory period of

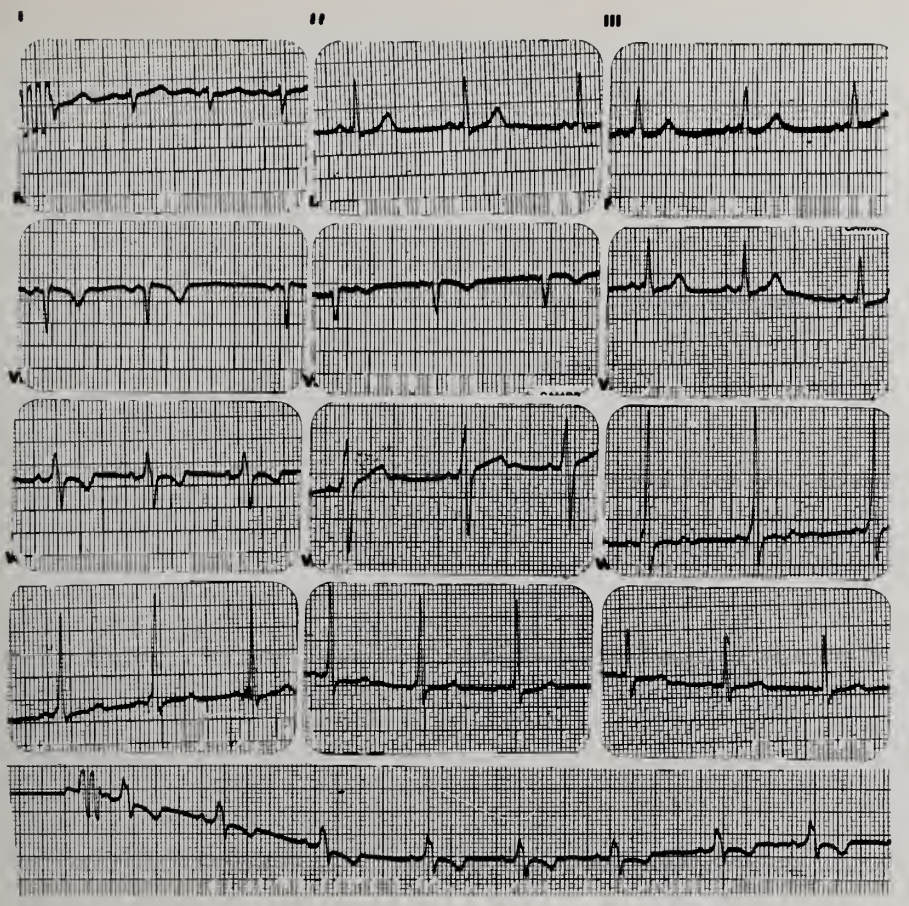


Figure 3.—Electrocardiogram recorded twelve hours after electrical conversion of tachyarrhythmia, revealing a marked decrease in ST-T abnormalities.

350 milliseconds reported in subjects without AV node disease.[3] Pronounced shortening of AV refractory period would be expected in the presence of catecholamine release, however, antegrade bypass fiber conduction is more probable.

The occurrence of functional cardiac arrest in an otherwise apparently healthy male during an extremely rapid supraventricular tachyarrhythmia is of interest. This observation is in contrast to other reports of cardiac arrest due to ventricular fibrillation in patients with W-P-W syndrome.[4-6]

Ventricular fibrillation during atrial fibrillation in W-P-W patients has been postulated to be due to preexcitation of the ventricles per bypass fibers early in the phase of incomplete ventricular recovery. The tracing in the present case, however, demonstrates atrial fibrillation with very rapid ventricular response due to antegrade bypass conduction and hemodynamic failure due to the rapid rate with possible dissociation of electrical and mechanical events.

Summary

A case is presented of functional cardiac arrest due to Type A Wolff-Parkinson-White syndrome with atrial fibrillation and ventricular response averaging 338 beats per minute and approaching 400 beats per minute. The arrest responded promptly to direct current cardioversion and only two further episodes of 10 minutes' duration with spontaneous conversion has been noted since institution of maintenance propranolol therapy.

REFERENCES

1. Misra S, Duvernoy WFC, Breneman GM: Atrial flutter with 1:1 conduction. Supplement to Circulation LXIV:202, Oct 1971

2. Friedberg EK: Diseases of the Heart, Third Ed. Philadelphia and London, W B Saunders Company, 1966, p 631

3. Linhart JW, Braunwald E, Ross J Jr: Determinants of the duration of the refractory period of the atrialventricular nodal system in man. J Clin Inves 44:883-890, 1965

4. Touche M, Jouvet M, Touche S: Arch. des Mal du Coeur Fibrillation ventriculaire au cours d'un syndrome de Wolff-Parkinson-White Réduction par choc électrique externe. Arch des Mal du Coeur 59:1122-1133, Jul 1966

5. Okel BB: The Wolff-Parkinson-White syndrome. Am Heart J 75:673-678, May 1968

6. Ahlinder S, Granath A, Solmer S, et al: Wolff-Parkinson-White syndrome med paroxysmalt atrieflimmer övergaende i ventrikelflimmer. Nordisk Medicin 12:1336-1338, 1963

Refer to: Cloninger P, Thrupp L, Granger GA, et al: Immunotherapy with transfer factor in disseminated coccidioidal osteomyelitis and arthritis. West J Med 120:322-325, Apr 1974

Immunotherapy with Transfer Factor in Disseminated Coccidioidal Osteomyelitis and Arthritis

PAUL CLONINGER, MD
LAURI D. THRUPP, MD
GAYLE A. GRANGER, PhD
HAROLD S. NOVEY, MD
Irvine, California

TRANSFER FACTOR (TF), first prepared by Lawrence from human lymphocytes,[1] is a chemical moiety with a molecular weight of less than 10,000. It is dialyzable and unaffected by ribonuclease, deoxyribonuclease and trypsin.[2]

TF has been used in treating diseases in which cellular immunity is deficient. A few patients with congenital immune deficiency states such as Wiskott-Aldrich syndrome, severe combined immunodeficiency disease and dysgammaglobulinemia, have improved following therapy with TF.[3] TF has been administered to patients with infectious diseases in which cellular immunity is deficient. Examples of such diseases are candidiasis,[4-6] lepromatous leprosy[7] and disseminated tuberculosis.[8] It also has been used in attempts to restore cellular immunity in diseases with acquired cellular immune deficiency states such as sarcoid and carcinoma.[9,10]

Coccidioidomycosis is one of the fungal diseases in which the primary site usually is minimally symptomatic or asymptomatic pulmonary infection without progression of disease. Healing of this primary process is associated with the development of cellular immunity as manifested by a delayed hypersensitivity reaction to intradermal testing with coccidioidin antigen. Failure to manifest delayed hypersensitivity in a patient with disseminated disease has been associated with a prolonged clinical course despite chemotherapy. The following case is that of a patient who had disseminated coccidioidomycosis with osteomyelitis who was not responding to amphotericin B therapy. He had remained anergic for several months, and then was treated with transfer factor.

From the Departments of Medicine and Medical Microbiology, University of California, Irvine, California College of Medicine.
Submitted August 9, 1973.
Reprint requests to: H. S. Novey, MD, Allergy-Immunology Division, Department of Medicine, University of California, Irvine, California College of Medicine, Irvine, CA 92664.

Report of a Case

A 24-year-old man of Spanish-American extraction was admitted to hospital after four months of progressive swelling involving multiple joints. In the week before admission chills and fever and drainage from the right ankle had developed. The patient denied intravenous use of drugs, venereal disease, trauma or antecedent arthritis. He had not traveled outside the Los Angeles-Orange County area for ten years.

The temperature on admission was 38.8°C (102°F). The pulse rate was 132 and regular. Ankles, knees, elbows, and the right wrist had tender, swollen, fluctuant and erythematous areas of varying severity. Laboratory data on admission to hospital included hemoglobin of 9.8 grams per 100 ml, and 13,500 leukocytes per cu mm with 78 percent polymorphonuclear cells, 18 percent lymphocytes, and 4 percent eosinophils. The erythrocyte sedimentation rate was 61 mm in one hour (Westergren). Blood urea nitrogen was 11 mg and serum creatinine 0.7 mg per ml. An x-ray film of the chest was normal. Radiographs of all the involved bony areas, as well as both femurs and ischium, were interpreted as showing diffuse osteomyelitis with bone destruction. Coccidioides immitis was cultured from aspirates or drainage from the right hand, left elbow, both knees, both ankles, the left foot and from bone marrow. The intracutaneous test to coccidioidin 1:100 was negative (Table 1) and the complement fixation antibody titer against coccidioidin was positive at 1:2048.

Therapy consisted of administration of amphotericin B, surgical excision and drainage, and appropriate antibiotics for several bacterial superinfections. After a month of such therapy, and 1.5 grams of amphotericin B administered intravenously, the patient's serum creatinine was 1.3 mg per 100 ml and creatinine clearance was 50 ml per minute. At the fifth month the creatinine clearance had declined to 28 ml per minute. The patient was febrile. Body weight had dropped to 80 pounds from a normal of 150 pounds. Cul-

TABLE 1.—*Results of Intracutaneous Tests for Delayed Hypersensitivity before and after Administration of Transfer Factor*

Skin Test	DATE								
	7/70	11/70	2/71	1/71	3/71	4/71	6/71	3/72	7/72
TF Administration			×			×			
Coccidioidin (Cutter) 1:100	0	0		0	0		E=20 mm I= 5 mm	E=? I=19 mm	E=60 mm I=19 mm
PPD 5 US units (Connaught)	0	0		0	..		..	0	0
Histoplasmin (Parke-Davis) Standardized	0	0		0	..		..	0	0
Mumps (Eli Lilly) 2 CF units	..	0		0	..		..	I=15 mm	I=10 mm
Trichophyton 1:30 (Hollister-Stier)	..	0		0	..		..	..	0
Dermatophytin 1:100 (Hollister-Stier)	..	0		0	..		..	..	..

×=Date administered.
0=Negative result (No induration or erythema).
..=Not tested.
E=Erythema.
I=Induration.

tures positive for C. immitis were still obtained from draining lesions.

The complement fixation titer decreased one dilution to 1:1024, and skin tests to both 1:100 and 1:10 concentrations of coccidioidin were still negative.

The decision was made to employ transfer factor immunotherapy in an attempt to improve cellular immunity to C. immitis because of the deteriorating condition of the patient and the evidence of renal toxicity from amphotericin. For this purpose an extract* obtained from 1 unit of blood donated by a coccidioidin hypersensitive donor was used. No evidence was provided for activity of this material. Following this administration of TF there was no conversion of the coccidioidin skin tests. However, the patient's clinical status stabilized and no new drainage area appeared. A second dose of TF was administered two months after the first. This material was prepared at our laboratories with 500 ml of blood from another donor. (See Methods.)

When skin tests were applied six weeks after the second administration of TF, a positive coccidioidin skin test was obtained for the first time (Table 1). The patient was discharged to a convalescent home and for the next six months continued to receive amphotericin but at a reduced schedule, as suggested by Winn when renal toxicity is a factor.[12] The maintenance dose of 40 mg of amphotericin B administered intravenously every third week was interrupted for six weeks, followed by a mild relapse with fever, pain and tenderness in the right elbow. C. immitis was cultured from an aspirate of the involved site. The lesion gradually healed after weekly administration of amphotericin therapy was resumed.

Three months later, 21 months after his original admission, the patient had received a total of 6.335 grams of amphotericin B. Creatinine clearance values were between 18 and 22 ml per minute. The coccidioidin skin test remained positive and the complement fixation titer had decreased to 1:256. The patient felt well, and there was radiographic evidence of healing of the bone lesions. At this point amphotericin was discontinued.

In the 16 months of follow-up, the patient remained free of symptoms except for a small draining lesion on the right wrist which cultured C. immitis, but which cleared spontaneously. He regained most of his lost weight and felt well. Some residual joint deformities and limitation of motion remained.

Methods

Transfer Factor Preparation

A coccidioidin-positive donor was located and a unit of blood was obtained. The red cells were removed from the whole blood by sedimentation for several hours at 4°C (39.2°F). The buffy coat was removed, and the cells washed several times in 15 millimols of sodium chloride. Then they were suspended in a small quantity of distilled water, frozen and thawed a total of five times and dialyzed against 50 ml of distilled water

*1.8 ml was provided by Dr. Peter Baram, University of Chicago.

TABLE 2.—*DNA Synthesis† and LT Production from Purified Peripheral Blood Lymphocytes Cultured with Antigens and Mitogens in vitro before and after Treatment with TF.*

Stimulants	*Before Admin. of TF (Skin Test Negative)*	*After 1st Dose of TF (Skin Test Negative)*	*After 2nd Dose of TF* (Skin Test Positive)*
PHA 30 μg	37,577 CPM±12%	32,010	50,357±10%
PWM .01 ml	17,481 CPM±10%	17,647	22,781±12%
Coccidioidin 0.01 ml	1,201 CPM±20%	872	1,372±15%
Coccidioidin 0.05 ml	876 CPM±30%	998	4,577± 8%
Coccidioidin 0.1 ml	1,205 CPM±23%	1,510	4,763± 7%
Histoplasmin 10 μg	987 CPM±20%	1,213	897±30%
None	1,105 CPM±20%	939	1,041±30%
LT production	0	0	+

*Prepared from a different donor than the first dose of TF.
†Incorporation of H^3 Thymidine.

DNA = Desoxyribonucleic acid
LT = Lymphotoxin
H^3 = Tritium
PHA = Phytohemagglutinin
PWM = Pokeweed mitogen
CPM = Counts per minute, H^3 thymidine incorporation

for 24 hours. The dialysate was shell frozen, lyophilized to dryness and reconstituted to a total volume of 2 ml with distilled water. The salt concentration in the TF sample was adjusted to physiologic levels. All procedures were performed under aseptic conditions.

Immunological Studies

Screening immunologic tests were done. These included intracutaneous tests, serum complement fixation tests and tests of the response of the patient's lymphocytes to various stimuli. The patient's lymphocytes were tested *in vitro,* before and after injection of transfer factor, for the capacity to synthesize DNA and produce lymphotoxin (Kramer and Granger[11]).

Results of Immunological Studies

Results of immunological studies are summarized in Tables 1 and 2. *In vitro*, the patient's lymphocytes responded to phytohemagglutinin (PHA) and pokeweed mitogen (PWM), but did not respond to three levels of coccidioidin, and produced no lymphotoxin. One dose of TF produced no change in the skin test or in lymphocyte reactivity. After a second dose of TF, which was prepared in our laboratory from the blood of another donor, the skin test converted, coccidioidin-induced lymphocyte DNA synthesis increased fourfold and lymphotoxin was produced. These apparent improvements in immunologic responses occurred during the same period that amphotericin was being administered and the patient was beginning to improve clinically.

Discussion

Morbidity and mortality rates associated with disseminated coccidioidomycosis have been high, with an overall mortality of 50 percent reported before amphotericin B became available.[12] With amphotericin therapy, the outlook is better.[13-17] In one review of 42 patients with disseminated coccidioidomycocis who were treated with intravenous amphotericin B, 82 percent had rapid and significant therapeutic responses. The dose range in 30 of these successfully treated patients was from 0.9 gram to 6.92 grams, with an average total dose of 2.47 grams.[18] The patient in the present case received 6.33 grams.

About 20 percent of disseminated coccidioidomycosis involves bone.[15] In one series 43 patients had coccidioidal involvement of the bones. Of these patients 21 were treated before 1957 and therefore did not receive amphotericin B. Eight of this group died, three had persistent drainage and ten were apparently cured. Of the 22 patients treated with amphotericin B after 1957, 19 were completely cured, one had persistent drainage and two died.[15] It is therefore apparent that therapeutic failures to treatment with amphotericin B still occur, and interference with normal renal function is an ever present danger.

Dissemination may be attributable to the virulence of the pathogenic organism, to the size of the infecting dose or to impaired host resistance. That the patient studied in this report is of Spanish-American descent may have accounted for lower resistance, since the incidence of dissemination is greater in darker skinned people for unknown reasons.[18,19]

Once dissemination occurs it is evident that the usual defense mechanisms, in particular the immunological ones, may be overwhelmed. Whether the patient in this case had a pre-existing defect in his immune defenses which facilitated dissemination is not known. Humoral antibodies of the precipitin and complement fixation types are produced in large amounts, while specifically sensi-

tized thymus-dependent lymphocytes are difficult to detect. These thymus lymphocytes presumably help destroy the invading organism while the antibodies may interfere with this activity by blocking access of the foreign antigens to the lymphocyte receptors.

Disseminated coccidioidomycosis, especially in the meningeal form, is well known for protracted courses of exacerbations and remissions. The disease can remain quiescent for long periods and engender false hope of a cure. Evaluation of any other treatment is therefore difficult. In the case of transfer factor immunotherapy, the problem is compounded by several unknown factors. To list only a few, there is the lack of knowledge of chemical structure, standardization of assay methods and specificity of action. In its favor, TF is apparently non-toxic and non-antigenic. It is hypothesized that in some unknown way TF from a coccidioidin skin test-positive donor stimulates the recipient's thymus lymphocytes to proliferate and attack C. immitis antigens either by direct contact or by the secretion of lymphokines such as lymphotoxin. Therefore, co-treatment with a fungicidal agent and TF may serve complementary aims. It could lessen the antigen load by destroying the growing organisms and also enhance cellular immunity by stimulating the production of specific thymus lymphocytes.

Progression of active lesions of coccidioidomycosis despite doses of amphotericin in the range of renal toxicity appears to be logical indication for immunological intervention in the form of transfer factor administration. A single trial, although a start, cannot confirm the efficacy of such an approach. Controlled studies are needed, as well as a method of standardizing the preparation and dose schedule of transfer factor before a definitive judgment can be made.

Summary

A patient with disseminated coccidioidomycosis involving the bones was moribund despite doses of amphotericin B in the renal toxicity range. He remained anergic to coccidioidin. After the second administration of Lawrence's transfer factor (TF) in an attempt to reconstitute the patient's cellular sensitivity to coccidioidal antigen, the patient improved clinically. *In vivo* and *vitro* tests for cellular immunity to C. immitis became positive.

It is not known whether these favorable changes were the result of TF immunotherapy or coincident with it. The effectiveness of such therapy will remain uncertain without controlled trials in patients with disseminated fungal disease and standardized TF assays.

REFERENCES

1. Lawrence HS, Al-Askari S, David J, et al: Transfer of immunological information in humans with dialysates of leukocyte extracts. Trans Assn Amer Physicians 76:84-91, 1963

2. Baram P, Mosko MM: Chromatography of the human tuberculin delayed-type hypersensitivity transfer factor. J Allergy 33: 498-506, Nov-Dec 1962

3. Levin AS, Spitler LE, Stites DP, et al: Molecular intervention in genetically determined cellular immune deficiency disorders. J Clin Invest 50:49a, 1971

4. Rocklin RR, Chilzren R: Transfer of cellular hypersensitivity in chronic mucocutaneous candidiasis. Monitor *in-vivo* and *in-vitro*. Cell Immunol 1:290, 1970

5. Kirkpatrick CH, Chandler JW, Schimke RN: Chronic mucocutaneous moniliasis with impaired delayed hypersensitivity. Clin Exp Immunol 6:375-385, Mar 1970

6. Uhr JW, Landy M, Ed: Immunologic Intervention. New York and London, Academic Press, 1971, p 23

7. Bullock WE, Fields JP, Brandriss MW: An evaluation of transfer factor as immunotherapy for patients with lepromatous leprosy. N Engl J Med 287:1053, 1972

8. Whitcomb ME, Rocklin RE: Transfer factor therapy in a patient with progressive primary tuberculosis. Ann Int Med 79: 161, 1973

9. Lawrence HS, Zweiman B: Transfer factor deficiency response—A mechanism of anergy in Boeck's sarcoid. Trans Assn Amer Physicians 81:240-248, 1968

10. Oettgen H, Old L, Farrow J, et al: Effects of transfer factor in cancer patients. J Clin Invest 50:71a, 1971

11. Kramer JJ, Grander GA: An improved *in vitro* assay for lymphotoxin. Cell Immunol 3:144-149, 1972

12. Winn WA: The treatment of coccidioidal meningitis. Cal Med 101:79, Aug 1964

13. Colwell JA, Tillman SP: Early recognition and therapy of dissemintated coccidioidomycoses. Am J Med 31:676, 1961

14. Winn WA: The use of amphotericin B in the treatment of coccidioidal disease. Am J Med 27:617, 1959

15. Iger N, Larson J: Proceedings of second coccidioidomycoses symposium, Phoenix, Ariz, Dec 8-10, 1965, Univ of Ariz press, 1967

16. Caudill RG, Smith CE, Reinarz JA: Coccidioidal meningitis. Am J Med 49:360, 1970

17. Sanford WG, Rasch JR, Stonehill RB: A therapeutic dilemma. The treatment of disseminated coccidioidomycoses with amphotericin B. Ann Int Med 56:553, 1962

18. Richter HS: Coccidioidomycoses: A report of 300 new cases. G.P. 39:89-93, Feb 1969

19. Willett FM, Weiss A: Coccidioidomycoses in Southern California: A report of a new endemic area with a review of 100 cases. Ann Int Med 23:349, 1945

LETTERS *to the Editor*

An "Open Book" Recertification Examination

To the Editor: I have recently submitted to the American Board of Dermatology, Inc., and Frederick A. J. Kingery, MD, President of the American Academy of Dermatology, Inc., a detailed proposal for a change in Board requirements. The subject deals with reforms that would satisfy the growing demand for recertification and/or relicensure from the public, the politicians, the third parties, and many dermatologists. The proposed change would demonstrate who are the highly qualified, up-to-date clinical dermatologic experts. I would like to suggest the concept is applicable to all physicians, Board certified or not.

In this short letter I shall not review the current standards for all Board eligibilities and/or retentions of said Diploma. The revisions I have suggested are as follows:

(A) All participants eligible for Board examination would take a Clinical Specialists Examination to be given perhaps in April (i.e., late in the formal Residency or training periods). The Clinical Specialists Examination would be nearly comparable to the current examination to become a Board diplomate.

(B) Those earning the Clinical Specialists Diploma could then apply for the specific Board Diploma of his Specialty without further examination. However, by doing so he would contract to take an "Open Book" Recertification Examination on a biennial or other reasonable time basis. The Open Book Recertification Examination would be based upon the contents of the major journals in the given specialty for the time period to be covered by the examination. If it is not taken or is failed, the Diploma and the diplomatic status would be lost only to be regained by retaking the Clinical Specialists Examination. Obviously some mitigating circumstances may allow temporary postponement. All Board Diplomates would then be basically qualified Specialists and their continuing expertise would be proven by periodic recertification. Thus the Diplomate would stand out from the self-proclaimed specialists to any interested parties.

The above proposals need not be introduced by radical upheaval. Present Diplomates should be allowed to continue as is or volunteer to join the new program by taking the Open Book Recertification Examination. The current, otherwise qualified, non-diplomate should also be allowed to take the Clinical Specialists Examination and be given the opportunity to contract for a Board diploma. The proposal would enhance and give an opportunity to many physicians for economic, energy conserving, self-directed current information updating free from distractions frequent to other modes of continuing education.

We must recall that today's public wishes to know our competency continues after our formal education ends.

David L. Weinberg, MD
San Bruno, California

Cluster Headaches—A New Treatment

To the Editor: Cluster or histamine headaches are rather uncommon and of unknown cause. They are of excruciating intensity and unilateral. They usually affect the frontal, orbital and temporal regions. There is throbbing, but usually no nausea or vomiting. There is no family history such as in migraines. The treatment of these headaches has been quite varied and without much success. Ergotamine products, antihistamines, periactin, analgesics, steroids, histamine desensitization and psychotherapy are among the therapeutic modalities used.

Since the cause of the pain is a vasodilatation of the external carotid vascular system and perhaps some of the branches of the internal carotid arteries, it is thought physiologically sound to pursue a therapeutic approach which would cause an immediate and powerful vasoconstrictor effect. Epinephrine seemed the logical drug. It is both an alpha and beta adrenergic agent.

The use of this drug on seven patients proved to be efficacious in all but one of the seven patients. The pain was effectively relieved after the treatment with epinephrine was initiated. The cycles were altered so that less episodes occurred and with much less intensity.

This new approach seems to merit further investigation and under well controlled circumstances.

Albert V. Giampaoli, MD
San Jose

Clinical Pharmacists and Patient Care

To the Editor: Concerns for the future development and promotion of the rational use of therapeutic agents have been raised as the impact of the current and projected shortage of clinical pharmacologists and trends in the medical school curriculum were recently assessed.[1-3] Since it appears unlikely that the need for physician specialists with interest and expertise in the clinical investigation of drugs, adverse drug reaction surveillance, drug information analysis and the teaching of the principles of rational drug therapy can be met in the near future, it has been suggested that a clinical pharmacist perhaps can effectively provide the expertise and involvement in many of these areas.[4] The evolution of pharmacy education from a predominantly physical science and product-oriented curriculum toward clinical pharmacy,[5] with emphasis on the application of drug therapy knowledge, has significant implications for broadening the scope of pharmacy practice in the future. There is now emerging a new generation of clinically trained pharmacists capable of assuming more responsible and decisive roles as drug therapy specialists and able to transform their knowledge of therapeutics into significant contributions which directly influence patient care.[6]

Recently at the San Francisco General Hospital's Alcohol and Drug Detoxification Units, collaborative efforts were initiated by practitioners of medicine and pharmacy to explore and deal with the complex and formidable problems associated with the task of providing optimal drug utilization and therapeutic practice. To date the results have been most encouraging and productive as a clinical pharmacologist, pharmacist, neurologist, rheumatologist, residents, interns, medical and pharmacy students participate together in a variety of patient care, teaching and research activities. There are compelling reasons[7] why it would be extremely desirable that a pharmacist knowledgeable in the pharmacology, pharmacokinetic and biopharmaceutic properties of drugs and their clinical use be included in collaborative efforts with pharmacologists and physicians to promote the safe and rational use of drugs. It has been suggested that the expansion of the pharmacist's role beyond those associated with distributive functions to include activities such as providing primary or chronic health care maintenance is in the interest of meeting the demands of our health care delivery system for more effective use of professional resources. With clinical pharmacologists and physicians, the clinical pharmacist can effectively broaden the scope of efforts to promote rational drug therapy practice beyond the academic and research center into the community where the need for more efficient utilization of drug therapy is most immediate and critical.

As new directions are being charted in the health professions to meet the demands of our health care delivery system, more functional and realistic definitions of individual responsibilities and roles involving patient care will need to be considered by practitioners of medicine and pharmacy. Whether these newly defined responsibilities and roles are successfully implemented will depend upon the willingness of pharmacologists, physicians and pharmacists to work together on their development now.

Theodore G. Tong, pharm d
Charles E. Becker, md
San Francisco

REFERENCES

1. Dykes MHM: Clinical pharmacology. JAMA 223:1497-1498, Mar 26 1973
2. Csakey TS: Clinical pharmacy and pharmacology: Friends or foes? J Medical Educ 48:905-908, Oct 1973
3. Walton CA: Clinical pharmacology and clinical pharmacy: A necessary alliance for practical advances in rational drug therapy. J Clin Pharmacol 13:1-8, Jan 1974
4. Franke DE: Relationships between clinical pharmacology and clinical pharmacy. J Clin Pharmacol 12:384-399, Jul 1972
5. McCarron MM: An approach to the education of patient-oriented pharmacists. Am J Pharm Educ 35:396-400, Aug 1972
6. McKenney JM, Slining JM, Henderson HR, et al: The effect of clinical pharmacy services on patients with essential hypertension. Circulation 38:1104-1111, Nov 1973
7. Goyan, JE: The pharmacist and the physician. Calif Med 114:95-99, May 1971

Dextroamphetamine Therapy in Hyperactive Children

To the Editor: As the authors pointed out in the summary of their article [Greenberg LM, McMahon SA, Deem SA: Side effects of dextroamphetamine therapy in hyperactive children. West J Med 120:105-109, Feb 1974], there is indeed a profound influence upon personality organization which the dextroamphetamines may produce. Perhaps the point should have been made a little more strongly, however, that merely because a child is "hyperactive," this, per se, is no indication for the use of stimulant medication and in the cases in which they reported undesirable side effects, clinically it would appear that perhaps these were not the best candidates to have begun on stimulant therapy.

Perhaps of even more importance, however, it

should be noted that the side effects as reported are those that are seen quite commonly in what can be construed as high doses of Dexedrine® which these authors were using. The overwhelming majority of children in whom amphetamines are indicated will be responsive to doses in the neighborhood of 5 to 15 mg, given only once daily, and it is hardly surprising to see the type of effect that they note when they were using 10 to 20 mg, twice daily. Unfortunately, it is side effects of this nature which have given many lay people such a bad impression of medication for what is such a common problem; namely, these normally preventable side effects which may be related to injudicious prescription of improper compounds but more particularly to injudicious use of excessive doses.

MICHEL D. STEIN, MD
Campbell, California

Informed Consent

TO THE EDITOR: As a physician performing frequent cerebral arteriography and facing this issue, I am compelled to comment in response to Dr. Rosenberg's excellent article on informed consent. [Rosenberg SH: Informed consent—A reappraisal of patients' reactions (Medical Jurisprudence). Calif Med 119:64-68, Nov 1973].

There seems to me to be an assumption on the author's part that *medically* the cerebral arteriogram is in the patient's best interest—with which I concur. And the further assumption that *medically* the risks of the procedure are outweighed by the benefits. I agree with the second assumption as well. However, despite the available percentages, I believe that once the *probabilities* of such complications are made clear to the patient, the weighing of risks should be the patient's judgment, for *he* is the one to bear the consequences.

In other words, I believe that patients should retain the right to "abuse" themselves and refuse to undergo procedures in which they do not feel the risk outweighs the benefit *to them.*

Conversely, I think the physician is arrogant and short-sighted when he resents the patient's refusal on informed consent. The patient's *medical* best interest should not be confused with his *general* best interest. That decision is beyond medicine and the physician. It is highly subjective and ultimately must rest with the patient only.

RUSSELL B. SADLER, MD
San Bernardino, California

Acupuncture

TO THE EDITOR: The article [Lewin AJ: Acupuncture and its role in modern medicine. West J Med 120:27-32, Jan 1974] by Dr. Andrew Lewin on acupuncture seems to depart from that scientific objectivity which is supposed to be the basis for modern medicine. Since when does an article from the "New Chinese News Agency" provide the type of documentation we need for a rational approach to medicine?

When the author makes a statement such as "a large proportion of surgical morbidity is due to complications of anesthesia, rather than to the procedures themselves," this reader is inclined to look with scepticism at the rest of his thesis.

If he really wants to promote the investigation of the mechanisms and uses of acupuncture, Dr. Lewin would do well to use only a reliable bibliography and to refrain from the use of irrational statements as to the need for this investigation.

REUBEN J. BALZER, MD
Walnut Creek, California

* * *

The Author Replies

I agree with Dr. Reuben J. Balzer's contention that the New China News Agency, as well as several others of the references cited, cannot be considered incontrovertible scientific sources. However, at the time the article was written reliable bibliographic material was not available. For this reason, I was very careful to state that the validity of the material and the reliability of the sources were definitely in question. In the last year under the auspices of the National Institutes of Health as well as many private organizations, research has begun on the efficacy and pathophysiologic mechanisms of acupuncture. Future articles will no doubt be able to rely on more definitive sources.

There is no point in arguing about the quantitative contribution of anesthesia to operative morbidity and mortality since data collection and interpretation of this problem are subject to multiple errors and biases. The basic point I was trying to make was that by avoiding general anesthesia in poor risk patients, a reduction in morbidity and mortality should be able to be achieved.

ANDREW J. LEWIN, MD
Los Angeles

Refer to: Root I, Ogden W, Scott W: The medical investigation of alleged rape. West J Med 120:329-333, Apr 1974

Special Article

The Medical Investigation of Alleged Rape

The web of human entanglement resulting from the cry "rape" may twist and disrupt the lives of the persons involved. The physician who is prepared and able to deal with the forensic medical aspects of the problem can play a vital role in the determination of innocence or guilt. And, if he is prepared to recognize and deal with the psychologic problems, the emotional distress and the anxiety, the physician can provide invaluable help.

IRVING ROOT, MD, WENDELL OGDEN, MD, *and* WAYNE SCOTT, MD
San Bernardino, California

THERE ARE FEW WEBS of human entanglement more complex than that woven by the cry "rape." The medical and legal investigations to determine what is or is not deceit are attempts to unravel the central and more visible portion of this web. Rape is a crime seldom witnessed by an impartial, unbiased observer. Therefore, it can be anticipated that the available statements will conflict. Just how complex this situation is can be illustrated by the fact that all the physical findings resulting from rape may also be found as a result of lawful consenting sexual activity.

Rape has been defined as the unlawful carnal knowledge of a female without her consent. These three factors, carnal knowledge, unlawfulness and lack of consent, must be shown individually in every case. Medical evidence may be necessary to establish carnal knowledge, and may help to show lack of consent, but it is generally of no value in judging unlawfulness. Here as in the entire field of forensic medicine,[1] the final answer should result from a multilateral approach involving medicine, law enforcement and the legal profession. The summation, the determination whether rape actually has been committed, is the responsibility and obligation of the courts, not of the medical profession.

The medical examination of the alleged rape victim is unique in medical practice. Its primary purpose is to provide medical information for legal investigation and action. Lack of competent, conscientious medical examination frequently will hinder or perhaps even negate any subsequent legal proceedings.

Unlawfulness in part depends on marital status and age. Sexual activity by a married couple is not unlawful and therefore there can be no rape in marriage regardless of the wife's consent or the nature of the act. Also, there is a statutory age of consent which varies from state to state and below which consent is invalid. Intercourse in such a situation constitutes statutory rape unless the couple is married.

Consent is defined by Webster as "The voluntary accordance with or concurrence in what is done or proposed by another; acquiescence; approval." But clearly it is easier to define this concept in the abstract than in the concrete. In de-

From the Department of Pathology, University of California at Irvine and the San Bernardino County Coroner's Office (Drs. Root and Scott); and the San Bernardino County General Hospital (Dr. Ogden).

Reprint requests to: I. Root, MD, 1890 North Waterman Avenue, San Bernardino, CA 92404.

termining consent in alleged rape, without the help of witnesses or documents and generally with diametrically opposed statements by the participants, the court is often faced with a formidable decision.

In the aftermath of alleged rape, the physician is called upon to answer medical questions in his field of expertise. Some appreciation and understanding of the problem as a whole should make his assistance to the court more valuable. For instance, he must assiduously avoid expressing in either his medical records or testimony an opinion as to the innocence or guilt of either party in this action. Such a statement could significantly impair his effectiveness as an expert.

A less visible, though perhaps more complex part of the web is the personal and emotional complications of alleged rape that may fundamentally alter the lives of the two persons involved. Here the physician is well equipped by training and experience to provide assistance. His value is proportional to his ability to recognize and treat the emotional problems as they arise.

The Medical Examination

In the medical examination of alleged rape, a rape examination check list (Table) is recommended. It provides a convenient reminder of important features to be noted, and also serves as a permanent medical record. Since there is a good possibility that this record also will become a legal document, the value of a complete and detailed record is clear. It is possible that the attorneys may agree to the use of good medical records in court, at least in the preliminary hearing, and make a court appearance by the physician unnecessary. In any case, a good deal of embarrassment and confusion can be avoided if these records are thorough. This is particularly true when time has elapsed between the medical examination and the testimony and memory has become cloudy and hazy.

There may be need for medical care in addition to the examination. This might include treatment of physical trauma as a result of the assault, prevention or treatment of venereal disease and the prevention or interruption of resultant pregnancy. Emotional trauma also may be a significant problem. The physician should be prepared to recognize it and either offer treatment or refer the patient for counselling service.

The initial items in the recommended check list are to provide positive identification of the

A Check-List to Use in Examination for Alleged Rape

Name of patient _____ Age _____

Address _____ Phone _____

Date examined _____ Hour____ Location____

Brought to hospital by whom _____

Name of peace officer _____ Badge No.____

Department _____ Phone____

Name and signature of R.N. assisting with Examination _____

I. Circumstances of alleged rape _____
   Details of attack—when, where, how (date and time) _____
   Who? _____ Known?____ Name(s) _____
   Unknown, more than one assailant, description of assailant(s) _____
   Previous coitus _____ Date____ Time____

II. Post alleged rape activities—douched, bathed, changed clothing, medications, other treatment (circle appropriate and note time)

III. Physical evidence
   Extragenital areas _____
   Genital areas _____
   Evidence of drug influence _____
   Evidence of venereal disease _____
   Evidence of pregnancy _____
   Last known menstrual period _____

IV. Emotional attitude: appropriate or inappropriate to findings _____

V. Laboratory evidence obtained (circle appropriate)
   A. Clothing: damaged, suspicious stains, given to peace officer, not applicable
   B. Hair samples
      1. Loose hairs adhering to patient or clothing
      2. Semen encrusted pubic hair
      3. Clipped pubic hair of victim (at least ten, labeled pubic hair)
   C. Semen specimen
      1. Swab or swabs from any suspicious stains (thigh, abdomen, elsewhere)
      2. Vaginal pool
         a. Wet smear examined by examiner: sperm present, sperm absent, motile, nonmotile
         b. Pap smear—to pathologist—labeled and sealed
         c. Acid phosphatase
   D. Blood, urine or other specimen for drug analysis

VI. Physician's clinical impression _____
   Signed _____MD State License No.____

VII. Treatment and disposition _____

VIII. Disposition of evidence
   Delivered by _____ Date____ Time____
   Received by_____ Date____ Time____

patient and the investigating officer, if the case has been referred by a law enforcement agency. As the form also indicates, a nurse should be present during the entire examination and her name should be recorded. The physician should keep in mind that this may be a false allegation of rape. If the patient has lied once, there is the chance she may do so again and the doctor may find himself faced with unwarranted charges.

The history in this situation is similar to any medical history because it constitutes the basis on which subsequent observations and interpretations are made. However, the history in any potential forensic medical problem also is somewhat different from the routine medical examination because it must be taken with an open, even a suspicious mind. The history may indicate a violent physical attack and struggle. Are the injuries consistent with the history and is the appearance consistent with the time interval? On the other hand, the history may indicate only threats of violence. Were drugs of any sort, including alcohol, used or administered which might in some way render the woman incapable of resisting or giving valid consent?

When did the episode occur? Was it in the previous few hours or was it some days or even weeks earlier? Where did it occur? Was it in some location where telltale evidence might be left on the clothing, such as in a grassy area or in bare dirt or gravel? How many assailants were there and can the patient identify them? When did she last have coitus apart from this episode? This last factor may have an effect on the interpretation of subsequent findings.

Inquiry should be made into the details of the sexual contact itself. Although this may be embarrassing to the patient, it certainly should be less embarrassing than talking to police officers or attorneys who undoubtedly will ask similar questions in intimate detail. Again, the answers may be significant in light of subsequent findings. Was a condom used? Was there penetration of the penis into the vagina and to what extent?

Activities after the alleged rape such as douching, bathing, changing clothes or ingesting drugs, medications or alcohol, are not unusual and their history is important in interpreting subsequent findings. The absence of motile or any identifiable vaginal pool sperm or of semen smears about the body even in a recent assault are understandable if the patient has douched or bathed before the medical examination. The absence of damaged or torn clothing, even though the assailant reportedly tore away the clothing, is understandable if the patient has changed clothing before the examination. However, if she did, where is the clothing? Is the clothing still available?

Are there abrasions, lacerations or teeth marks about the breasts, face, genitalia or other portions of the body that might tend to confirm a vicious, forcible assault? Is there evidence that the patient might be under the influence of drugs, including alcohol? Such an observation could indicate the need for laboratory tests to identify the type and quantity of such drugs. The finding of drugs may well have some modifying effect on the legal interpretation of the alleged rape.

Evidence of venereal disease or pregnancy a length of time after the alleged attack may corroborate that coitus actually occurred. Finding out when the last known menstrual period occurred may indicate how much attention should be given to the possibility of an ensuing pregnancy.

Is the emotional attitude or affect of the patient appropriate or inappropriate to the history and physical findings? The examiner should be aware that the alleged victim of a rape will undergo extensive, pointed and often embarrassing questioning before and after the medical examination itself. In truth, the woman will be required to prove her own innocence. For the innocent victim, this is a very traumatic and emotional ordeal. If the woman appears to be distraught, emotionally upset or frightened, this would tend to support her story. Conversely, a casual or almost nonchalant attitude after an allegedly vicious and forcible attack might cause some doubt about the truth of the history.

In the presence of the nurse, the doctor should observe the patient as she undresses, examining the outer and under clothing for damage or suspicious stains. The examination of this clothing after it has been removed is frequently more difficult to interpret. The clothing should then be given to the police officer as a part of the physical evidence. Detailed examination of this clothing remains the job of the criminalist.

Although human hair does not provide positive identification that finger prints do, it may be used to exclude persons from consideration as suspects. Loose hairs adhering to the patient's body or clothing should be packaged separately, labeled and given to the police. For comparison purposes, at least ten clipped pubic hairs from the victim should be packaged separately and labeled "pubic

hair." Suspicious moist or dried stains should be scraped, the scrapings placed in separate small containers, identified as to their location and origin, and given to the police.

A wet smear of vaginal pool material, preferably with a drop of saline solution, should be examined fresh by the examiner for the presence of sperm. If sperm are present, the quantity (whether rare, moderate or numerous) should be noted and also the presence or absence of motility. Sperm motility may be expected up to four hours in the vagina.[2] A delay in this examination could result in a false negative interpretation. It is particularly desirable that the physician analyze this specimen himself in order to make his records as comprehensive as possible and to avoid the necessity of bringing yet another witness into court.

The fixed vaginal pool smear for cytologic examination (Papanicolaou smear) should be submitted to the pathologist for further study. Not only is this of value in finding sperm when only small numbers are present, but it also may be valuable for morphologic findings. Rarely, an individual may produce significant numbers of abnormal spermatozoa and this fact could help identify or clear a suspect. Of course, the absence of sperm does not rule out the possibility of recent intercourse, since the suspect may be an oligospermic or aspermic person either as a result of a vas ligation, some other physical situation or use of a condom. Additionally, testing the vaginal pool specimen for acid phosphatase may be useful in indicating the time interval since intercourse has occurred. A significant prostatic acid phosphatase level is indicative of prostatic secretions and although the level may decrease relatively rapidly, it may remain positive for up to 18 hours.[2,3] The acid phosphatase specimen should be frozen immediately if the examination in the laboratory is to be delayed.

Obtaining a specimen of blood, urine or gastric contents should also be considered to confirm the presence of alcohol or other drugs indicated by the history or physical findings.

The positive identification of any specimen obtained for laboratory examination may have important legal implications. For this reason, identification of all specimens is essential. Smears should be prepared on frosted end slides on which the physician has written in pencil the patient's name, his own name or initials and the date. Pencil markings will withstand the subsequent processing and staining whereas almost any other means of marking, including indelible pencil, may be washed away. A glass marking stylus, although a means of positive indelible identification, is generally not available. A minimum of handling of any specimen by messengers or other intermediaries is desirable. In each instance, a written receipt and record should be prepared to accompany the specimen.

As in any medical examination, the conclusion should be the physician's clinical impression. Is there evidence that coitus has occurred? Are the physical and laboratory findings consistent with the history or is there a discrepancy? *The physician cannot and should not state whether the patient has been raped. Rape is a legal, not a medical, definition.* The physician should discuss his conclusions with the investigating officers. There is, however, no need for the physician to confront the patient with what he feels are discrepancies in his findings.

Consent

Although some of the findings of the medical examination may be useful in evaluating the question of consent, the final determination must be made by the courts. There will be two versions of the event, one from the alleged victim and one from the alleged assailant. One may be completely true and one false or there may be some truth in both. The facts may be similar in both versions but with different interpretations. To sort out fact from fiction is the function of our legal system, an adversary system in which both parties present their respective versions and interpretations and an impartial judge or jury makes final determination.

The charge of rape may result from a number of circumstances. For instance, it may stem from the action of a true criminal, whose continued freedom constitutes a real menace and danger to society. Because of his potential continuing threat, this person must be apprehended quickly and dealt with in the most effective manner possible for the protection of society.

Or the charge may stem from an act of intercourse culminating a night of progressive involvement and love-making. The couple may have started with drinks and dinner, then had more drinks until both were intoxicated and their judgment impaired. At this point intercourse may have been attempted. Although alcohol may increase the desire and lower the inhibitions, it may also impair the capability to the extent that full

erection or orgasm cannot be reached. Nevertheless, carnal knowledge is defined as penetration to the slightest extent of the vagina by the penis and requires neither full erection nor ejaculation. It is difficult to judge, then, if there was consent, implied consent or no consent.

The charge of rape also might arise from a disagreement over a matter of expected or implied compensation. On the other hand, the situation might involve a true love affair where the girl is not of legal age of consent and yet where there is every intention by the couple to marry some day. Her parents may learn of this affair, disapprove of the man and institute rape proceedings. The District Attorney is as obliged to prosecute a case of this kind as he is a case involving a criminal rapist. Or the woman may bring a false accusation where there has been intercourse with full consent, or perhaps no contact at all, as a means of getting even for some real or imagined slight or injury.

In short, there are many and varied circumstances in which the facts are open to interpretation and a fair decision is difficult to reach. Even when the final conclusion has been reached that rape was committed, the question of how severe the penalty should be must be considered in light of the circumstances of the act.

The Personal Element

Although they are not emphasized in the legal dispute, mental anguish, emotional distress and feelings of guilt may become of overwhelming significance to the persons involved. In recognizing this fact and seeing that his patient receives professional guidance or care, the doctor provides a badly needed service.

Throughout the detailed police investigation and the intensive questioning on the stand by the attorneys, the woman who has been raped in private will be figuratively raped in public. She is subjected to the most intimate scrutiny by the public and by her friends, neighbors and acquaintances. Did she really resist? Did she really try to protect her honor? Or did she in some way encourage the accused? She may no longer be regarded in the same light as before, and this can have significant impact on her home life, marital life and other interpersonal relationships. The experience may be so traumatic that it causes her to drop the charges in an effort to avoid more emotional stress. She may need help to voice these feelings, as well as gentle understanding by the physician.

In many ways the impact on the man falsely accused may be just as devastating. If he is married, the publicity of the investigation and court proceedings may disrupt and even destroy his family life. It may have a significant effect on his business life. If he is a professional person, such as a teacher, doctor or lawyer, doubts may be raised about his moral character and this can affect his ability to obtain a license or practice his profession. Anxiety or other emotional disturbances may ensue. There often may be lingering doubts in the minds of family, friends, associates and acquaintances that are not dispelled regardless of the legal outcome. These shadows can haunt the lives of either or both the accuser and the accused indefinitely.

REFERENCES

1. Root I, Scott W: The clinician and forensic medicine. Calif Med 119:68-76, Sep 1973

2. Wecht CH, Collom WD: Medical evidence of alleged rape, Legal Medicine Annual. Appleton Century, 1969, pp 269-285

3. Enos WF, Beyer JC, Mann GT: The medical examination of cases of rape. J Forensic Sci 17:50-56, 1972

Refer to: Sheldon G: The role of hyperalimentation in patients with multiple injuries (Trauma Rounds). West J Med 120:334-337, Apr 1974

Trauma Rounds

Chief Discussant
GEORGE F. SHELDON, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is the second of a series of Conferences on Trauma at San Francisco General Hospital

The Role of Hyperalimentation in Patients with Multiple Injuries

DOCTOR TONY ROON:* The patient, a 43-year-old carpenter, received multiple rib fractures, laceration of the right lobe of the liver, fracture of the right acetabulum and flail chest in an automobile accident, June 9, 1973.

In the hospital to which he was admitted, treatment consisted of exploratory laparotomy with drainage of the liver laceration. The flail chest was managed by positive pressure ventilation. Dihiscence of the abdominal wound developed after operation and this led to further complications including five episodes of massive gastrointestinal hemorrhage. When the bleeding could not be managed conservatively, an 85 percent gastrectomy with a Billroth II gastrojejenostomy was performed. Further stress bleeding occurred and again medical management failed, necessitating revision of the gastroenterostomy and further gastric resection. The patient had originally weighed 242 pounds. After the multiple operations for stress bleeding, he lost 32 pounds in a period of one month. Because of his poor nutritional status, a feeding jejenostomy was carried out to augment alimentation. Shortly after that, gastrojejenostomy and the feeding jejenostomy broke down and both resulted in fistulae. In addition, multiple fistulae from the transverse colon and small bowel developed later (Figure 1).

The patient was transferred to the Trauma Service at the San Francisco General Hospital. He weighed 195 pounds, had multiple enterocutaneous fistulae and appeared to be in a relatively wasted condition. Management at first consisted of local skin care and institution of intravenous hyperalimentation. After ten days severe lower abdominal cramping pain developed. On exploratory laparotomy an outlet obstruction at the site of gastrojejenostomy was observed, as well as multiple small bowel fistulae and a colocutaneous fistula. The operative procedure consisted of transverse colectomy with hepatic flexure colostomy and resection of small bowel fistulae. Construction of a retro-colic gastrojenostomy permitted the use of the afferent limb to patch the fistula at the lesser curvature. Debridement and closure of the efferent loop fistula completed the procedure. The abdomen was closed with wire sutures, the skin being left open.

Hyperalimentation, 5,000 calories a day, was continued after the operation. The postoperative

*Assistant Resident Trauma Service.

Supported in part by NIH Grant GM 18470 and the Northern California Trauma Committee, American College of Surgeons.

Reprint requests to: D. D. Trunkey, MD, University of California Service, San Francisco General Hospital, San Francisco, CA 94110.

Figure 1.—Enterocutaneous fistulae with sump drainage.

course was stormy and breakdown of the gastrojejenostomy occurred again, but the patient did become anabolic and the wounds began to heal. As abscesses localized within the peritoneal cavity, they were definitively drained. The gastric fistula closed spontaneously ten days after the operation.

A month after admission oral feedings were begun, though they were supplemented by continued hyperalimentation. Gradually a changeover was made to a regular diet. Ambulation was restored over the next three weeks as the acetabular fracture healed, and at last the patient was sent home.

DOCTOR DONALD TRUNKEY:† *One of the major advances on our Trauma Service in recent years has been the use of hyperalimentation in patients with complicated depleting injuries. This, more than any other factor, has permitted successful salvage of patients of the type just presented. Dr. Sheldon, this patient certainly represents a triumph in metabolic management. As his attending physician, would you mind making some comments with regard to his treatment?*

DOCTOR GEORGE SHELDON:* This patient was very well cared for during the initial stages of management. He was resuscitated quickly, problems were recognized and he was operated upon early. The severe liver laceration was managed appropriately with direct suture ligation of bleeding vessels, and drains were placed. The acetabular fracture was reduced and immobilized and the flail chest injury was subsequently managed with a volume respirator.

The postoperative problems that developed after that are common in severely injured patients. Stress ulceration with bleeding is a constant threat, though fortunately medical management suffices in most cases. Since it was impossible to control the stress bleeding by conservative means in this case, operative intervention was carried out. The development of an enterocutaneous fistula and small bowel and transverse colon fistulae was probably ascribable to the catabolic state with decreased collagen synthesis and increased collagenase activity. Although hyperalimentation was begun in the hospital to which he was first admitted, some problems were encountered and the patient was referred to us.

DOCTOR TRUNKEY: *Doctor Sheldon, what is your indication for starting hyperalimentation?*

DOCTOR SHELDON: The metabolic management of severely injured patients begins in the Emergency Room. Gamble showed in 1939 that 5 percent glucose administration can spare approximately half the nitrogen loss the patient would ordinarily sustain following a severe injury. The best index

†Chief of Surgery, Mission Emergency Hospital, San Francisco.
*Chief of Trauma Service, and Hyperalimentation Service.

of when to start hyperalimentation is to project where he will be five days hence. If he is going to require nutritional supplementation and it is anticipated he may not be on a regular diet within five days, it is probably best to start hyperalimentation in the immediate postoperative period. If the patient has been severely injured, then some type of caloric supplementation should be started shortly after his resuscitation. Certainly it should be instituted within two to five days after the injury in any case in which the projected ability to take oral feeding is still questionable at this time.

DOCTOR TRUNKEY: *What do you think is the best way to achieve caloric supplementation?*

DOCTOR SHELDON: If the gastrointestinal tract is intact or access to a major portion of it can be obtained, then unquestionably this route is optimal. It has been shown that if you keep air out of the stomach you can feed some patients immediately after operation. We usually do not do this because of the danger of aspiration. When the integrity of the gastrointestinal tract is questionable, the easiest way to provide caloric supplementation is through the subclavian vein. This presupposes, however, a familiarity with the hazards of subclavian catheterization and the three kinds of complications that may result: (1) Mechanical, due to placement of the subclavian line, (2) septic, due to contamination of the intravenous solution or due to local infection, and (3) metabolic, due to trace element or hyperosmolar characteristics of the solution.

DOCTOR TRUNKEY: *Having made the decision to use hyperalimentation, how does one proceed?*

DOCTOR SHELDON: In our hospital, ten to fifteen patients a day receive intravenous hyperalimentation. Hyperalimentation is initiated in consultation with the hyperalimentation service which is composed of the surgeon from the trauma service, a surgical nurse, and a pharmacist. A senior resident places the subclavian line. This technique requires the care accorded to the placement of a cardiac pacemaker. Sterile technique is essential.

An x-ray film is taken after placement to confirm subclavian position and rule out pneumothorax or other mechanical complications. Care must be taken to advance the needle and catheter together lest the catheter be sheared off by the needle, with catheter embolus resulting. The patient should be in Trendelenburg position to preclude the hazard of air embolism.

Once placed, the line is used only for administration of the hyperalimentation solution. Commercial preparations available consist of protein split products, usually hydrolysates of casein or fibrin. Free amino acid solutions are also available. No product is clearly superior. They vary in composition. It behooves one to know the trace elements and electrolyte composition of the solution used, and there may be some advantage in changing the type of solution from time to time in any one patient to provide a wider spectrum of trace elements.

We begin with a mixture composed of 10 percent dextrose and 5 percent protein. This solution is advanced daily as tolerated to 20 percent dextrose and 5 percent protein, which contains roughly 1 kilocalorie per ml. We push the solution to the maximum tolerated without glycosuria. If the patient has pancreatic insufficiency, he may require insulin but it is not routinely used.

Patients should have certain laboratory tests conducted daily (see Protocol in adjoining column). The most crucial are fractional urine determinations, blood urea nitrogen and body weight. If fractional urine determinations coupled with intermittent determinations of blood sugar are monitored carefully, hyperosmolar coma can be avoided.

Prevention of septic complications is essential, starting with good aseptic technique during placement of intravenous lines. We believe that all solutions should be prepared by a specially trained pharmacist using a laminar air-flow hood. Cultures should be taken regularly as part of the routine. The pharmacist is also responsible for preventing solution incompatibility and precipitation.

With careful attention to asepsis, we change the subclavian site three times a week. In addition, once every 24 hours we change the intravenous tubing between the containers of solution and the subclavian catheter, and we use a 1 micron filter in the intravenous line, though these two procedures have not been proved to be essential. In their entirety, however, these methods have kept our catheter sepsis rate to less than 5 percent. It is known that the solutions are hyper-

PROTOCOL FOR PARENTERAL HYPERALIMENTATION

1. Baseline studies to obtain before starting hyperalimentation: electrolytes, hemoglobin, hematocrit, blood urea nitrogen, bilirubin, SGOT, alkaline phosphatase, blood sugar, calcium, phosphorus, magnesium, albumin, prothrombin time.

2. Daily studies until the patient's course stabilizes (five to seven days):
   (a) Fractional urine every six hours
   (b) Blood sugar
   (c) Electrolytes
   (d) Accurate intake and output of liquids
   (e) Body weight

3. Routine laboratory work after the patient's course has stabilized:
   (a) Daily: Intake-output, body weight, fractional urine
   (b) Two to three times weekly: electrolytes
   (c) Once a week: blood cell count, platelet count, prothrombin time, BUN, creatinine, calcium, phosphorus

4. Recommended schedule:
   (a) Day 1: 2 bottles protein in 10 percent dextrose solution
   (b) Day 2: 2 bottles protein in 15 percent dextrose solution
   (c) Day 3: 2 bottles protein in 20 percent dextrose solution
   (d) Advance number of bottles of protein in 20 percent dextrose as patient's condition warrants.

5. Avoid sudden discontinuing of the solution. Taper off along the same schedule as the initiation schedule.

6. If temperature spikes above 38.3°C (101°F) occur:
   (a) Discontinue the catheter, filter, line, and solution and start an entirely new set-up.
   (b) Culture the catheter tip at the time of removal. This requires cleaning of antibiotic cream from catheter site with an alcohol sponge. Remove the catheter and insert into holding media. Clip off tip with sterile scissors.
   (c) Culture the filtered hyperalimentation fluid. Attach sterile needle to a line below filter and run 10 ml of fluid into each (screw cap) sterile culture tube.
   (d) Culture the hyperalimentation bottle. Disconnect tubing from the bottle. Place a sterile intravenous bottle medication cap (or other sterile covering) over the bottle top and send all the remaining solution for culture.

osmolar and have a low pH, which provides optimal growth conditions for Candida Albicans.

DOCTOR TRUNKEY: *What do you use as an index of anabolism?*

DOCTOR SHELDON: The best index of anabolism is a bed scale. If the patient is gaining weight without evident edema, then most likely he is in positive nitrogen balance. Often we are called in consultation to see a patient who is receiving 3,000 calories a day on a hyperalimentation program and is not gaining weight when his physician assumes he should be. Despite the apparent caloric load, it is simply a fact that the calories are not adequate. Many patients require 4,000 to 5,000 calories before converting to an anabolic state.

In the present case, even when the patient was receiving 5,000 calories a day he did not really add weight until the last of the abscess cavities was drained. Caloric requirements will vary from patient to patient, depending on the amount of injury, fever, sepsis, and other factors. Blood urea nitrogen determinations are a useful index of anabolism. As it is the breaking down of proteins that accounts for a measurable BUN, if you give a patient a 24-hour load of substrates consisting of glucose and amino acids, then the blood urea nitrogen will tend to be low when anabolism occurs. When he is no longer tearing down his endogenous proteins the BUN will usually fall to between 4 and 6 mg per 100 ml.

DOCTOR TRUNKEY: We will conclude on the note that intravenous hyperalimentation constitutes a major advance in the management of critically injured patients. The indication for hyperalimentation of this kind is the inability of the patient to take nourishment enterically. When it appears that the patient's injury will interfere with adequate caloric intake, intravenous supplementation should be instituted. Septic complications should be avoided by careful placement and sterile protection of a subclavian central venous line. A 5 percent protein hydrolysate is added to a 10 percent and then 20 percent dextrose mixture—the latter providing approximately 1,000 calories per liter. Anabolism is recognized by weight gain and a fall in blood urea nitrogen. As much as 8,000 calories a day may be required to put the patient in positive nitrogen balance.

Refer to: White KL: Caveats for PSRO's. West J Med 120:338-343, Apr 1974

Caveats for PSRO's

KERR L. WHITE, MD, *Baltimore*

As MATTERS STAND NOW, it seems probable that Professional Standards Review Organizations (PSRO's) will base their assessments on specific standards of practice promulgated locally, regionally or nationally, and that these standards will serve as the basis for taking corrective, perhaps punitive, action against practitioners who fail to meet them. While most physicians would agree that our profession must strive relentlessly to improve the services we provide, and many of us believe that broader accountability is inevitable, the PSRO prescription as currently being discussed may well be a recipe for chaos. There are five assumptions underlying this scheme that should not go unexamined. These assumptions are:

1. Practitioners in the United States are distributed bimodally with respect to their clinical competence—that is, there are "good doctors" and "bad doctors" and we know how to tell them apart. It seems to be assumed further that the "good doctors" will be the ones to say which are which.

2. Medical practice is more usefully assessed in relationship to "diagnoses" and "processes" than in relationship to "performance" or "outcomes" of patient care.

3. Contemporary medicine has a substantial number of clearly defined and well-understood preventive, diagnostic and therapeutic forms of intervention for which the clinical efficacy and patient care utility have been objectively assessed by means of randomized clinical trials or other credible evidence, and we know precisely what to do for the majority of the most common health problems brought to the medical profession.

4. Health information systems now exist that will permit objective statements to be made about the adequacy of care given to a specific patient by a specific practitioner at a specific time and place.

5. Sub-optimal patient care, however defined and measured, is due more to the inadequacies of the individual practitioner than to failures in the organization of health care systems or institutions or to the inappropriate allocation of priorities and resources by society.

There are, in addition, three objectives underlying the concepts of "standards for practice," and the PSRO legislation in particular, which should be stated so that all can appreciate what is being discussed:

1. The overall costs of health care both individually and collectively should be contained, if not reduced.

2. There should be a relatively uniform, minimal level of expectation with respect to the clinical efficacy and patient utility of medical care for all citizens.

3. Equity of access, or "fair shares," should characterize the setting of priorities and the allocation of national, state and local resources for health care.

In other words, the essential problem with respect to health care policy and the setting of so-called "standards of practice" is to balance costs, quality and equity. This is always the task in any effort to restructure health services.

Finally, by way of introduction, it should be

Based on remarks made at the Fall Meeting of the Institute of Medicine, National Academy of Sciences, November 15, 1973.

The author is Professor of Medical Care and Hospitals, The Johns Hopkins University, Baltimore.

Reprint requests to: K. L. White, MD, Department of Medical Care and Hospitals, The Johns Hopkins University, School of Hygiene and Public Health, 615 North Wolfe St., Baltimore, MD 21205.

understood that in talking about objective assessments and even about measurement, we mean the assignment of numbers to objects, attributes or events according to rules; we are not talking about the kind of assessment of quality embodied in the aphorism: "Mirror, mirror on the wall, who are the best clinicians of them all?" My comments, therefore, will be based on the assumption that we are concerned with improved measurement, or even any reliable measurement, as a basis for decision-making referrable to standards, normal values, deviations and sanctions.

Now, with respect to the first assumption, namely that there is a bimodal distribution of overall clinical competence for the entire practicing profession, let me start by saying that I know of no evidence that would support this assertion. We have no idea about the shape or skew of the distribution of clinical competence; we do know something about the ability to answer examination questions and about the frequency with which some procedures, operations and treatments are employed. However, even if a bimodal distribution could be identified or even if the lowest 5 percent of practitioners on a normal distribution were classified as "bad doctors" by the "good doctors," is it desirable to place our emphasis on punishing or correcting the "bad doctors" or is it better to put the emphasis on helping the other 95 percent to improve the level of their practice? I would argue that our efforts should be put on strengthening those aspects of medicine that are good and helping those physicians who most of the time make every effort to do their best, rather than on the small number of "bad guys" who should be unfrocked because of fraud, chicanery or overt incompetence.

Most of the efforts to date with respect to evaluation of Medicare and Medicaid, and even the work of some of the Foundations for Medical Care, have been concerned with fraud and chicanery and very little with assisting the great bulk of practitioners to improve the care that they provide. If we have limited resources to devote to improving the quality of care through PSRO activities, I suggest that the emphasis be placed on information and education for the majority, not punishment for the few "rascals" and "incompetents" among us. An educational and behavioral posture toward the medical profession on the part of the profession itself rather than a punitive or even "corrective" posture seems central to attainment of the three overall objectives with which most, I think, would agree.

Surely one of the central features of any profession is its capacity to evolve and adapt in response to society's needs. If this assertion is wrong then the potential, if not the performance, of continuing education, and perhaps of medical education itself as a basis for a lifetime of learning, needs to be reexamined carefully.

The second assumption states that medical practice is more usefully assessed in relationship to "diagnoses" and "processes" than in relationship to "outcomes" of care. It is the functional result as reflected in the individual and collective capacity of patients to perform and produce after receiving medical care that counts, not what procedures or treatments are employed. A diagnosis is only a means to an end; of itself it has little discernible medical utility and no social utility. At best it is all too frequently a hypothesis that requires testing. This is particularly true at the level of primary care and frequently at the level of secondary care.

However, of much greater moment is the realization that patients do not present at the level of primary care or even at the levels of secondary and tertiary care with "diagnoses"; they present with symptoms, complaints and problems for which they seek relief. The task of medicine is to resolve the problems that are first perceived by patients as "headache," "pains in the chest," "rashes," "stomach pain," "backache," "unusual bleeding," "cough," "weakness" and "fatigue" and the hundreds of other symptoms that initiate the demand for medical care and constitute the language of disease.

If our guides or requirements for the management of specific diseases and diagnoses are based on the "process" approach and characterized by lists of prescribed procedures derived from the contemporary collective wisdom of "experts," then I think we run the serious risk of encouraging five undesirable trends:

1. *Defensive medicine.* There will be a tendency for physicians, particularly those who are less secure and in the greatest need of support and education, to carry out the full range of prescribed procedures so that they minimize the risk of "corrective" action.

2. *Cookbook medicine.* Individual clinicians

will be encouraged to work by the book, to follow the authoritarian pronouncements of the "experts" and to use the Merck Manual approach for the care of patients, rather than to accept the professional risks and intellectual rewards of developing and applying their clinical knowledge and acumen in the best interests of specific patients. The cookbook approach to medicine would seem to me to be anti-intellectual and should be vigorously discouraged. It could stultify and fossilize clinical practice and stifle its evolution.

3. *Normative medicine.* The threat of sanctions will encourage all physicians to move toward the mean values or to remain within some range that reflects central tendencies. One only has to recall the conventional wisdom of the past with respect to normal deliveries, myocardial infarctions and hepatitis to realize the possible tyranny of slavish adherence to all contemporary standards.

4. *Hazardous medicine.* The greater the number of procedures carried out and the longer the patient is in hospital, the greater the risk of misadventure. The object of any clinical exercise should be to relieve the patient of his complaint or distress as rationally and rapidly as possible with the minimum number of procedures and the shortest possible institutional involvement. In at least one study, 20 percent of the patients experienced some hazardous episode and 7 percent died as a result.[1] A hospital is a very dangerous place to be if the benefits do not outweigh the risks!

5. *Inflationary medicine.* Cost containment requires that we be more selective in the procedures done, and on balance, do fewer, not more; and that we reduce hospital days used, not increase them. If "process" standards are prescribed, it seems highly probable that this will considerably increase the number of procedures and hospital days. New demands on laboratories, radiology units and record rooms are bound to exacerbate manpower shortages as well as inflate costs, and they cannot be justified in the absence of evidence that improvement in the health care or health status of the population will result.

Let me give some practical examples: By what standards do we judge a general internist in a town of 25,000 people with a 100-bed hospital when faced in his office by a 50-year-old housewife with vague intermittent upper abdominal pain and an alcoholic husband, or when faced by a 35-year-old auto mechanic with vague chest pain of two weeks' duration? Medicine at this level is still largely probabilistic, not deterministic, and the individual decisions in each case may be based on historical, behavioral, social and clinical evidence that is infinitely more relevant at the first encounter with these two patients than would be a gastrointestinal x-ray survey, a gall-bladder series or an electrocardiogram. How do we assess care objectively at this level? At present we do not even know the distribution of these common problems in the populations of patients seen by physicians in different practice settings.

The real test of the clinician is the extent to which his patients are returned to work or school, kept out of bed, relieved of functional impairment or pain and freed from the use of unnecessary or useless drugs. These are the measures that really count as far as the patients and public are concerned—and, I would add, as far as the bulk of the medical profession is concerned.

The third assumption affirms that we have a substantial number of efficacious procedures that have been evaluated by randomized clinical trials or on the basis of long and wide experience, and that we have benefits which clearly outweigh any attendant risks, hazards or costs. In the latter category, I would put streptomycin for tuberculous meningitis and not vitamin B-12 for backaches.

First, it is essential to distinguish between the three functions of preventing, curing and caring. Second, we need to identify those forms of preventive, diagnostic and therapeutic intervention that are clearly beneficial and for which problems and under what conditions they are beneficial. This alone should free enormous amounts of money and resources for the caring function, much of which seems to be the indirect benefit of the placebo and Hawthorne effects. These are scientific and educational exercises for the long haul to which some segment of the medical establishment should address itself aggressively.

I doubt that any accurate account exists, but I would be very surprised if more than a quarter of all the tests, procedures and therapeutic regimens imposed on specific patients are more beneficial and useful than they are harmful or useless, and the figure may be lower. It would be important to know. The efforts to improve quality and reduce costs should be directed at educating practi-

tioners to undertake fewer procedures of dubious value and encouraging them to improve their clinical expertise.

To stimulate discussion, let me suggest alternative ways in which the middle-aged woman and the young man described above might be treated by a physician and end up in both instances by being relieved of their symptoms. The first involves two or three visits in the course of a month or two, a wait-and-see, probabilistic approach, supported by one or two tests or x-ray studies done with the patient ambulatory, while the second involves several days in the hospital and a vast battery of diagnostic and therapeutic procedures. It might well be argued that the burden of proof is on those who would favor the latter approach to patient care as representing better care. Yet this is what we will be encouraging if we promulgate "expert" standards for management of "chronic cholecystitis" and "coronary artery insufficiency"—the diagnostic labels we use to justify hospital admission and insurance coverage.

The fourth assumption asserts that we have national, regional, state and local health information systems to generate the necessary knowledge for making sensible decisions about the competence of the individual practitioner's care of his individual patients. This is not the time or place to discuss the conceptual and technical problems of health care information systems and the work that lies ahead of us in developing an adequate network of such systems in this country.[2]

A few comments are indicated in the present context, however. One possibility widely mentioned in PSRO discussions is the use of the length-of-stay standards produced by the Professional Activity Study (PAS) hospital discharge abstract system of the Commission on Professional and Hospital Activities. While the commission deserves great credit for its pioneering efforts, it should be clear that there are a number of limitations to the usefulness of PAS data. What is not fully understood is: (1) the hospitals participating in PAS volunteer to do so, on the basis of enthusiasm, interest or need, (2) they are concentrated in the 200 to 500 bed category and (3) they account for only about 25 percent of the short-term nonfederal hospitals of the country and 40 percent of their 36 million discharges annually. However, the numbers involved are much less important than the fact that the hospitals are not a statistically representative sample of all hospitals in the country and hence of all practices. It would be misleading from a statistical and logical point of view to generalize to the national experience, let alone regionally or locally from these kinds of data. It should also be understood that the validity and reliability of PAS length-of-stay standards depend upon the individual performance of the many medical record rooms who supply the basic data. Many serious reservations have been voiced about the quality of these data and in at least one recent study of a large metropolitan hospital, they were found to be totally inadequate.[3]

What is needed as the basic health information system for the description of health care currently being given, at least at the level of the hospital, is the universal application of the Uniform Hospital Discharge Data Set and the related terms, definitions and classification schemes, through decentralized hospital discharge abstract systems that measure regional patterns and reflect regional needs. There are about a dozen of these regional systems now in operation across the country (including several based on the PAS system) and the terms of the basic data set have been officially promulgated by the United States National Committee on Vital and Health Statistics and endorsed by the American Hospital Association.[4,5] These 14 "bits" of information can generate a large number of critical tables that would inform practitioners and administrators alike about the health care system of the country in the ways that Florence Nightingale advocated more than a century ago.[6]

This approach to the development of information about health care recognizes the principles of parsimony and utility in the expensive collection of data about patient care. It is more sensible to carefully collect a little information on the entire universe of patients or the population at risk than to haphazardly collect a great deal of data of uncertain validity and reliability from a limited group of patients admitted to selected volunteering hospitals. Particularly if we are to have so-called national standards or even regional and local standards, they must be based on the objective collection of credible data and the generation of useful information that describes the full range of hospital experience. If we can agree that standards should not be based on authoritarian pro-

nouncements of experts who see a selected segment of the sick people of the country, or on "normative" rates from unrepresentative samples of patients or hospitals, then we should start with the universal recording of a prudent amount of comparable empirical data that has some chance of being analyzed and understood at national, regional, state and local levels.

We have the knowledge and expertise in this country to develop these systems and to use them effectively. Let me give some examples. It would be more informative to compare measures such as case fatality rates, lengths of stay, rates for selected diagnostic and therapeutic procedures, rates for selected complications, and mean total charges per admission (as a proxy measure of the intensity and complexity of care) among hospitals and among all hospitalized residents of counties, states, medical catchment areas, regions and the nation, than to focus on specific aberrations of physicians in specific cases. There is nearly always an explanation for clinical activities associated with individual cases when they seem unusual by some external standard. By contrast, the initial "belling of cats" is usually much easier when directed at hospitals or groups of institutions or systems than at individual physicians and their individual patients. By aggregating credible data that will describe the performance of institutions and the care received by population groups, those responsible for the distribution of health care resources and the allocation of priorities can see what and where the problems are before they attempt to identify individual practitioners as offenders in particular instances. The effect on an institution or a group of hospitals of information based on objective monitoring may be as large or even greater than the collective effect of individual sanctions, corrections or punishments directed at the physician; at least this is one possible conclusion based on an examination of one claims review system that has been carried out.[7]

It would, then, be preferable to examine small amounts of information based on universal coverage and to evolve information systems gradually than to embark on vast data collection exercises in an unsystematic fashion designed to feed computers and offend common sense.

The fifth assumption suggests that inadequacies in care are related more to "practitioner" failure than to "systems" failure. While some air crashes are undoubtedly related to pilot error, many more are related to systems failures and even here the attention given to the design of systems and the provision of redundancy far exceeds anything we have in health care. By focusing on the care given by groups of institutions like hospitals, Foundations for Medical Care or HMO's, and on the care received by populations defined by geography, we bring to light systems problems and the related issues of priorities, resource allocation, health insurance arrangements, incentives and managerial competence. This has the enormous advantage of informing the public and its representatives in the legislatures and on the boards of trustees, as well as the profession itself, about the characteristics of their health care systems and their impact on the individual actions of patients and physicians.

The pressure exerted on institutions to improve the collective and individual performance of physicians and other personnel is likely to be politically more palatable and operationally simpler than pressure applied on the small fraction of aberrant physicians who are described as "bad doctors." The emphasis would be on supporting and educating the great bulk of physicians and improving the general environment in which they work rather than on harassing individuals or segregating them for special comment. This can always be added later as circumstances warrant, but it seems a poor place to start from the point of view of overall needs.

In summary, I question the present emphasis on "process" standards directed at physicians' practices that seems to characterize much of the thinking about PSRO's because:

1. Much work needs to be done to separate efficacious procedures from the rest. For only a small proportion of the problems presented by patients at the level of primary care do we know enough to set "process" standards, or even to define what currently goes on.

2. Much more needs to be done to build up population-based, problem-oriented information systems that use data parsimoniously for making useful decisions about the medical care provided by hospitals and other health care institutions for the populations they serve.

3. The use of predetermined "process" standards based on data of uncertain validity collected from unrepresentative samples would, in my judgment, be anti-intellectual, unduly rigid, and dis-

courage clinical initiative, and would be potentially hazardous to patients and inflationary.

4. "Systems" failure may be as important or more important than "practitioner" failure if medical care is unacceptable with respect to access, quality and cost. We should focus on hospitals and systems before we focus on individual physicians and their individual patients.

5. An educational rather than a punitive approach is preferable if medicine is to maintain its professional traditions. Do we want to catch a few rascals, or do we want to improve medical care for all citizens?

REFERENCES

1. Schimmel EM: Hazards of hospitalization. Ann Intern Med 60:100-110, 1964

2. Murnaghan JH: Health services information systems in the United States today. N Engl J Med 290:603-610, 1974

3. Hendrickson L, Myers J: Some sources and potential consequences of errors in medical data recording. Meth Inform Med 12:38-45, Jan 1973

4. Murnaghan, JH, White KL (Eds): Hospital Discharge Data: Report of the Conference on Hospital Discharge Abstract Systems. Med Care 8:Supplement 1-215, 1970 and Philadelphia, J. B. Lippincott Co., 1970

5. United States Department of Health, Education, and Welfare. United States National Committee on Vital and Health Statistics. Uniform Hospital Abstract: Minimum Basic Data Set. Washington, D.C., Government Printing Office, 1972 (DHEW Publication No. HSM 73-1451)

6. Nightingale F: Hospital Statistics and Hospital Plans. London, Emily Faithfull & Co., Victoria Press, 1862

7. Buck CR Jr: Peer Review: The Impact of a System Based on Billing Claims. Baltimore, Maryland, Department of Medical Care and Hospitals, The Johns Hopkins University, (Sc D Thesis, processed) 1973

Treatment of Primary Breast Cancer: A Radiotherapist's View

This is how I would like to be treated when I get my carcinoma of the breast—and I am very likely to. My sister and my mother both died of carcinoma of the breast; hence my intense interest in it. On finding a lump, I would like to have mammography and thermography. I would not like anybody to rush me into any form of treatment. I would then like to have the lump excised and histologically examined by serial section to get a very good idea of the histological prognostic factors, because they are, in some cases, just as important as the clinical stage. One has to blend all the prognostic factors to get a good idea of what's going to happen to the individual patient.

After the histological examination, I would like to have metastasis excluded. I would like to have a bone scan in particular if my skeletal survey is negative, because I know of many patients whose disease showed up first in bone scan before there was obvious disease in the radiological films. Certainly this happens also in other diseases. This is not always true, but I would certainly have a bone scan if I had the least bit of discomfort anywhere in my body. I would like my doctors to consider all my other medical conditions, to evaluate my risks, my normal risks, if I didn't have that breast carcinoma. Also, I would like my doctors to inquire from me whether I had any fears of radiation, whether I had any fears of mutilation. I have many patients come, following mastectomy, who say to me, "I didn't mind the operation, but I feel like half a woman." I have had many complaints in this regard and my happiest patients are those who have had a local excision and radiation, regardless of what happens to them in the future. It's quality, not quantity, that matters. So I would like a decision made by a discussion among my physician, my surgeon, my radiotherapy consultant, but most particularly myself, because it's my body and I would like to be able to determine my risk if I have radiation, my risks if I have surgical operation, and all the possibilities that might ensue if I live 20 years. I probably won't, because I'm too old for that, but I would like to know all the possibilities. Many patients would not like to know this and they would not like to share in the decision, but I think there are many, many women who would but are afraid to tell their doctor. They don't get a chance to get past the barrier. Their doctor is up on a pedestal and they feel too meek and mild, but they come and tell me about it afterward.

—M. Vera Peters, Senior Radiotherapist, *Toronto*
Extracted from *Audio-Digest Surgery*, Vol 20, No. 2, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Refer to: Sanazaro PJ: PSRO and options for the future. (Informed Opinion). West J Med 120:344-347, Apr 1974

PSRO and Options for the Future

PAUL J. SANAZARO, MD, *Washington, D.C.*

THE TREND of the past ten years is evident; with the growth of federal expenditures for medical care has come a parallel growth in demand for accountability. Major organizations in the public and the private sectors of medical care are eager to display their ability to render such public accounting on behalf of the medical profession. PSRO is the only such opportunity reserved, by law, to the medical profession until 1 January 1976. But PSRO is only one of several actual or potential mechanisms for controlling utilization, while, to a greater or lesser extent, assuring its quality. What is not generally known is that both of these basic provisions were part of the original Medicare law of 1965. Because the Medicare law is administered by the Social Security Administration, utilization review was put into effect, but the requirement that staffs of hospitals conduct studies of the quality was never imposed. The major differences between the original provisions and the current law (PSRO) are: (1) physicians rather than a federal agency are given the responsibility for implementation; (2) the retrospective form of utilization review and its attendant retroactive denials are eliminated; and, (3) quality assurance must accompany utilization control.

It is also not generally known that the Secretary of Health, Education and Welfare currently has legal authority to appoint special review teams in each state for the express purpose of evaluating hospital and physician performance under the Medicare law. In addition, the Secretary of HEW has legal authority to impose stringent utilization review measures which would be administered by the Social Security Administration. The significance of these facts is that if PSRO were to be repealed today, there already exists statutory authority to substitute a more intensive type of review which will not then be under the control of physicians.

There are other efforts by voluntary organizations which parallel the intent of PSRO. One of these is the new requirement of the Joint Commission on Accreditation of Hospitals for a retrospective medical audit that concentrates on the outcomes of care. At present it is not known how this requirement will mesh with that of PSRO, but clearly some accommodation will have to be worked out. Also, in the voluntary sector is the Plan Utilization Review (PUR) of the Blue Cross Association. Under this proposal, Blue Cross Plans will use the criteria developed by local PSRO's to screen claims. Blue Cross would employ nurse coordinators to perform the second level of review by examining medical records. If the problem were not resolved by this step, Blue Cross would then refer the matter back to the local PSRO. It is the view of a fair number of individuals that a not-for-profit voluntary organization such as the Blue Cross Association can best mediate between the interests of the medical profession and those of the public. If PSRO were to

The author is Project Manager of Private Initiative in PSRO.

Private Initiative in PSRO is sponsored by the American Association of Foundations for Medical Care, the American College of Physicians, the American Hospital Association, the American Medical Association and the American Society of Internal Medicine, and is financed by a grant from The Kellogg Foundation.

Reprint requests to: P. J. Sanazaro, MD, Private Initiative in PSRO, 1776 K Street NW, Suite 400, Washington, DC 20006.

disappear, it is possible that PUR could establish itself as the dominant review program for Medicare.

There are other forces which will influence the type of assessment called for by PSRO. One of these is the new Health Maintenance Organization (HMO) legislation, which carries with it several hundred million dollars to be expended over the next three years. The relationship between PSRO and HMO is not fully explicit. Because PSRO had been enacted, Congress agreed that PSRO's would have authority to review the performance of HMO's with respect to utilization and quality. But Congress also appropriated large sums of money for research on quality of care in the HMO program. The original HMO proposal had called for the establishment of an independent Commission on the Quality of Care. This organization, while relating directly to the HMO's would be expected to become the public's national ombudsman in all matters of quality of care.

It is apparent then that PSRO is not an isolated example of a demand for accountability. What is unique is the legal provision that physicians take the initiative. Now, most physicians are concerned over what effect PSRO might eventually have on the practice of medicine. This can only be speculative at present, since there is not a single PSRO in operation in the United States. Before any extrapolations are made, we should examine the present status.

As of this date, final area designations will have been made. As soon as the federal machinery can be established, PSRO applications will be received and acted upon. It is important to realize that HEW has made an enlightened and unusual policy decision regarding the PSRO program: it will not issue regulations for the present. Doctors Simmons and Goran (Director and Deputy Director, respectively, of the Office of Professional Standards Review), recognizing how difficult it is to anticipate all the problems and opportunities in PSRO, have decided to issue a manual containing what in essence are guidelines. As experience is acquired with PSRO, these will be modified and gradually transformed into regulations. The manual, issued after review by the National Professional Standards Review Council, will constitute guiding policy for the initial funding and operation of PSRO's. The guidelines have been circulated in draft form. They are briefly summarized here.

PSRO's will be not-for-profit corporations, open to all licensed, active physicians in the designated area without regard for membership in any other professional organization. The PSRO must represent at least 25 percent of all such physicians. Physicians will constitute a majority of the governing board of the PSRO. As an organization, the PSRO will have appropriate standing committees and staff in order to oversee and conduct the required review procedures.

PSRO's will first be designated as planning or conditional, before they can become fully operational. In order to assist the average PSRO applicant, regional offices of HEW will make financial and technical assistance available to expedite organization and staffing. The regional office will make advance payments when the application has been approved. The most important activity during the planning phase will be the development of the formal plan of operation.

Upon completion of its formal plan, the applicant PSRO can qualify for conditional status. On receiving such an application, HEW will publish notice of its receipt in the *Federal Register,* local newspapers and appropriate journals. Congressmen, senators, mayors, governors, medical societies and voluntary health associations will be notified of the application. If fewer than 10 percent of the active physicians in the designated PSRO area register a protest, the application will be approved if the other conditions are met. If, however, more than 10 percent of active physicians object to the establishment of the PSRO, a formal mail ballot will be conducted of every active physician. A majority of those responding must endorse the PSRO in order for action to be taken on the application.

When designated as a conditional PSRO, the organization can then proceed to implement its formal plan. The most important principle in the formal plan is that the PSRO is responsible for all aspects of review conducted within its area. The PSRO may delegate some or all of the review to any individual, organization, institution, or association, but the PSRO retains the responsibility.

Initially, PSRO will review care in those institutions participating in the Medicare, Medicaid, and Maternal and Child Health programs. This will

predominantly involve short-stay general hospitals, but subsequently will include mental health institutions, tuberculosis hospitals, skilled nursing facilities, and intermediate care facilities. Extension of review to ambulatory care requires formal approval by the Secretary of HEW. In any event, initiation of review in short-stay general hospitals and skilled nursing facilities will be the main priority in the early phases of PSRO implementation.

Three basic types of review will be required: (1) admission certification; (2) continued stay review; and (3) medical care evaluation.

Admission Certification is simply the determination of the necessity for medical treatment in a hospital. Under ordinary circumstances it will be completed within 48 hours. The admission certification is based on explicit criteria which will be used in screening by designated non-physician personnel. The PSRO will designate which personnel perform this function. If admission is deemed necessary, an initial length-of-stay is to be assigned, most likely the 50th percentile for the particular diagnosis.

In the beginning, all elective admissions are to be certified in this manner. It is a matter of option for the PSRO to require pre-admission certification. It may do so in the instance of particular physicians, hospitals or diagnoses. The PSRO must also conduct admission certification for a sample of emergency admissions. The sampling must be carried out so as to be certain that particular problem areas are not overlooked.

Continued Stay Review or concurrent review has two co-equal components. First, it certifies the continuing medical necessity of care in the institutional setting. Second, it concurrently assesses the quality of care. Continued stay review is to be based upon explicit criteria where appropriate. These criteria are to be applied by personnel designated by the PSRO. Their function is simply to screen and to refer to physicians or the review committee any questions or problems not of a purely technical nature.

Medical Care Evaluation is equivalent to a retrospective in-depth audit of perceived problems in utilization or quality. This is visualized as a series of short studies, highly focused, to be conducted in a single hospital or a group of hospitals. The results of such studies must be reported to the PSRO along with evidence that the results have been used in planning continuing education. It is possible that the medical care evaluation requirements of PSRO will be very similar to the medical audit requirements of the Joint Commission.

In all forms of review mentioned, use is to be made of norms, standards and criteria developed by the local PSRO. The local PSRO will in all likelihood be given samples of these by the National Council, but the local PSRO must develop its own norms, standards and criteria for admission certification and for continued stay review.

The relationship of the local PSRO to individual hospitals within that PSRO area will be specifically defined. The PSRO must conduct an official evaluation of each hospital's capability for conducting the three types of review which have been described. The PSRO can delegate authority to the hospital for conducting one, two, or all three reviews, but PSRO retains the responsibility and must continually monitor the effectiveness of the hospital review activities. The norms, criteria and standards used by any hospital in conducting its own review are to be those of the local PSRO. If the hospital staff wishes to change these, and good and sufficient reason can be shown, exceptions will be permitted. The PSRO can delegate authority for review to a particular hospital only if the physicians of that hospital have participated in the overall review activities of PSRO, including the development of criteria. That is to say, in order to assure fair distribution of effort and uniformity of criteria based on local judgment, hospital medical staffs must be active within PSRO if those same staffs are to be eligible for certification of capability for conducting independent review. If such certification is granted, determinations by that hospital will be accepted as final by the PSRO, Medicare and state agencies. At that point, there will be no retroactive denials.

Many physicians fear there may be massive data requirements in PSRO. This could be costly and wasteful and could also serve to discredit the program if it literally drowned in its own data. HEW has again shown insight in suggesting that virtually all the information required by PSRO can be provided by manual tabulation. That is to say, there is at present no foreseeable need for subscribing to hospital abstracting systems in order to provide to PSRO the data that document decisions made, and changes occurring as a result of admission certification, continued stay review, and medical care evaluation.

This parsimonious approach to data applies only to the hospital phase of PSRO review. What the data requirements are likely to be, and how they are best handled in the ambulatory phase, is an extremely difficult question. There are no suitable answers to this at this time.

These, then, are some present realities of PSRO; and although these are only the sketchy beginnings, they are encouraging. The medical profession is being allowed a high degree of flexibility in implementing PSRO. It is clear that the local PSRO will be in firm control of whatever review is required. How to implement PSRO so as to avoid serious problems and pitfalls while realizing most of its desirable potential is a problem that is squarely in the lap of the medical profession. It is the kind of problem the profession should have had more often in the past.

My own projections of the future impact of PSRO on medical care are of course biased, and no more accurate than any list of expectations. First and foremost, PSRO should enable the profession to identify and install feasible and effective methods of continually upgrading the quality of care. This "leveling upward" of the quality should eliminate the deep valleys that unfortunately still exist. As a corollary, the medical profession should develop its own mechanisms for formally revising the criteria for the quality of care. As these criteria increasingly reflect scientific evidence regarding medical efficacy, they will become more and more uniform nationally.

Second, PSRO provides a vehicle for increasing the profession's public accountability, without violating confidentiality. Through appropriate partnership with the public in the PSRO effort, there should be much more widespread public understanding and appreciation of how the profession discharges its responsibilities in assuring quality while limiting unnecessary care.

One of the most tangible benefits of PSRO will be the creation of a physician organization which will become the equivalent of a Commission on Quality of Care for each state. Once these are effectively functioning, considerations of the cost of care will fall into proper perspective. These same organizations which generate important data on the content and use of care, can produce information of vital interest and importance to the Congress when it begins serious debate of national health insurance. At present, most assumptions regarding the best form of national health insurance are not backed by any hard data. PSRO will provide these crucial data, especially when it includes ambulatory care.

A fifth potential benefit of successful implementation of PSRO is that quality assurance can then be substituted for the several relicensure and recertification procedures now being widely discussed. Recertification is after all another response of the profession to the demand for public accountability. But, if the local PSRO can document that the quality of care in its area meets professional standards, then, by definition, physician performance must be satisfactory. There is then no need for still another activity to determine whether a practicing physician is professionally competent.

Except for improving the quality of care, PSRO is likely to have little direct impact of its own on how medical care is organized in the United States. I believe that PSRO can significantly improve the bargaining position of the profession with society in general on matters of accountability, and with the Congress in particular regarding national health insurance. None of this is for certain, because the stakes are high and there are no guarantees in this area of medical politics. But, they do seem to be the currently available options. How, and to what extent, organized medicine responds to these options will largely determine whether they can be realized.

Information

CLINICAL CARDIOLOGY SERIES

Suppressed Plasma Renin Activity and Primary Aldosteronism

PAUL I. JAGGER, MD

Material Supplied by the American Heart Association

THE APPEARANCE in the 1960's of a relatively simple radioimmunoassay for plasma renin activity (PRA) has resulted in the rapid increase of literature relevant to renin changes in hypertension. At the same time, this radioimmunoassay has made the measurement of PRA available for general use. Therefore, the physician who sees patients with hypertension needs to understand the significance of this recent literature in order to know when to use this tool.

Renin, of course, is the enzyme produced in the cells of the juxtaglomerular apparatus of the kidney that acts on a circulating substrate to initiate the formation of angiotension II. Angiotensin II is both a potent vasoconstrictor and a stimulus to aldosterone secretion by the adrenal cortex. The observation concerning renin that has received the most attention recently is the somewhat unexpected finding that as many as 25 percent of patients with hypertension have suppressed peripheral PRA. This means that PRA remains low even after the patient has been subjected to a stimulus that would increase PRA in the normal individual. The stimulus usually employed involves placing the patient on a low sodium diet for three to five days and then having him walk about for two hours.

Suppressed PRA has been emphasized in the past as a critical finding in patients with primary aldosteronism. Though this is true, it now has been shown that the majority of patients with suppressed PRA do not have aldosterone hypersecretion and an alternate explanation for suppression is needed in these cases.

Dr. Jagger is from the Department of Medicine, University of California, San Diego, School of Medicine.

Primary Aldosteronism

In primary aldosteronism, autonomous hypersecretion of aldosterone by a lesion in the adrenal cortex (classically, by an adenoma) results in increased sodium reabsorption by the distal renal tubule, leading to extracellular fluid volume expansion and hypertension. This expansion is "sensed" by the juxtaglomerular apparatus cells and their production and secretion of renin are suppressed. However, the fall in renin and, subsequently, in angiotensin II levels does not result in decreased aldosterone secretion as it does in the normal because the aldosterone secretion is autonomous. It is the combination of the suppressed peripheral PRA and the fixed high aldosterone level that confirms the diagnosis of primary aldosteronism.

Very rarely, an adrenal tumor can produce the precursor 11-deoxycorticosterone (DOC) instead of aldosterone and in these instances aldosterone levels will be low, but DOC levels will be elevated. Since aldosterone-stimulated reabsorption of sodium from the distal tubule takes place mainly in exchange for potassium, hypokalemia becomes a prominent feature in most patients with primary aldosteronism and the measurement of serum potassium provides a simple screening test.

Other Documented Adrenal Cortical Diseases

Peripheral PRA also is suppressed in two other well defined situations where there is documented steroid hormone excess, sodium retention, and hypertension. These are Cushing's syndrome and certain forms of the adrenogenital syndrome. In Cushing's syndrome the salt retaining effect of large amounts of glucocorticoids offers an adequate explanation for the suppression of PRA. However, increased production of mineralocorticoids also has been found in some patients. In the C-11 hydroxylase deficiency form of the adrenogenital syndrome there is increased production of androgens and of DOC and it is the DOC that causes sodium retention and PRA suppression. Patients with this form of the syndrome appear as masculinized females or precocious males with hypertension. In the C-17 hydroxylase deficiency form there is decreased production of both androgens and estrogens and, theoretically, increased production of both DOC and aldosterone. Actually,

however, only the DOC levels have been found to be consistently elevated. These patients present with poorly developed secondary sexual characteristics and hypertension. Of course, it is obvious that the diagnosis of Cushing's syndrome and of the adrenogenital syndrome usually is made on other grounds than the suppressed PRA.

Suppressed Plasma Renin Activity in Essential Hypertension

Jerome Conn postulated in 1964 that perhaps 20 percent of patients who, by all the usual criteria, had essential hypertension actually had "normokalemic primary aldosteronism." This provided the impetus for investigators to measure peripheral PRA in large numbers of patients with hypertension. It now is obvious that at least 20 percent do, indeed, have the suppressed PRA. However, as noted, most of these patients do not have elevated or fixed aldosterone levels. Neither do any significant number have Cushing's syndrome or the adrenogenital syndrome. A great deal of work is being done at present to determine why PRA is suppressed in the remainder. A defect in the sympathetic nervous system response to volume depletion has been offered as one explanation. It is more tempting, however, to implicate some unidentified type of mineralocorticoid excess in these patients. In support of the latter view, it has been shown that they do have expanded extracellular fluid volumes and that the inhibition of adrenal steroid synthesis by aminoglutethimide or the administration of the mineralocorticoid antagonist spironolactone can result in sodium and water loss and lowering of blood pressure. A search for other possible mineralocorticoids has led to the discovery by Melby and his associates of increased secretion of 18-hydroxy-11-deoxycorticosterone in a few, but certainly not the majority, of these patients.

An important additional factor in attempting to understand the significance of a suppressed PRA is the contention by Laragh and his associates that the finding of a suppressed peripheral PRA has important prognostic implications apart from any possible relationship to causes. Their data show that patients with hypertension and low peripheral PRA have a more benign course than those with normal or high peripheral PRA and that they are protected from the development of strokes and heart attacks. If this is confirmed by others it would not only offer another reason for the measurement of PRA in patients with hypertension, but also would imply that the treatment of hypertension should emphasize those antihypertensive drugs, such as alpha methyl dopa and propranolol, that suppress renin secretion.

Recommendation

The efforts to explain the significance of a suppressed PRA are still continuing and all the answers are not yet available. In the meantime a practical guideline is needed as to when the clinician should attempt to demonstrate, with sodium restriction and ambulation, suppressed peripheral PRA. In formulating this guideline the important point to emphasize is that at present the measurement of peripheral PRA in a patient who by all other criteria has essential hypertension probably will not lead to a cure of the hypertension, or to a drastic change in therapy. This being the case, it is recommended that the attempt to demonstrate suppressed PRA be limited for the present to those patients who have features that suggest the presence of the specific entity, primary aldosteronism. The most important feature, of course, is spontaneous hypokalemia. This recommendation, however, may change drastically if further causes of suppressed PRA are defined or if the prognostic significance is confirmed.

Diabetic Rehabilitation Center

A DIABETIC REHABILITATION CENTER has been opened at Sequoia Hospital in Redwood City, the nation's first in this regard. Its aim is to take individuals with complications of diabetes and give them sufficient knowledge and skill to manage their own problems. A thorough medical evaluation will be included as well as suggestions as to the appropriate direction of therapy. Special attention will be given to those who have visual impairment or blindness from diabetes, and vocational rehabilitation clients will be the major group served. The project is funded on an administrative basis through a grant from Health, Education, and Welfare and will encompass all of California, Nevada, Arizona, Hawaii and Micronesia. Interested persons should contact J. J. Prendergast, MD, Director, Sequoia Hospital Diabetic Rehabilitation Center, Whipple and Alameda, Redwood City, CA 94062. Phone (415) 365-0310.

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

HEREDITARY RETINAL AND CHOROIDAL DISEASES—Volume I—Evaluation—Alex E. Krill, MD, Professor of Ophthalmology, Pritzker School of Medicine, University of Chicago, Chicago. Harper & Row, Publishers, Medical Department, 2350 Virginia Avenue, Hagerstown, Md. (21740), 1972. 354 pages, $19.75.

It is so regrettable that this book is one of the last published writings of this outstanding vision scientist. Doctor Krill has written it in a very clear and succinct style, with an emphasis upon cause and effect and a correlation between structural changes and visual dysfunction. In this volume, the principles of genetics, the electroretinogram and the electrooculogram, and visually evoked responses are reviewed, with a helpful emphasis upon their clinical relevance. Friend and coworker, Desmond B. Archer, contributes an excellent chapter on the technique and interpretation of fluorescein angiography, with numerous illustrations of very good quality. Finally, evaluation of night vision—dark adaptation, and color vision tests are discussed, explained, and evaluated.

This book has an excellent bibliography. It is current and very useful for the clinician and others in the vision sciences.

ROBERT E. CHRISTENSEN, MD

* * *

DISEASES OF THE VULVA—Nikolas A. Janovski, MD, FCAP, MRC PATH (ENGLAND), Consultant Pathologist, Illinois Registry of Anatomic Pathology, Founding Fellow, International Society for the Study of Vulvar Disease, Department of Obstetrics and Gynecology, Passavant Memorial Hospital, Northwestern University, Chicago; Charles P. Douglas, MB, FRCOG, Professor and Chairman, Department of Obstetrics and Gynecology, Royal Free Hospital, School of Medicine, University of London, Founding Fellow, International Society for the Study of Vulvar Disease. Harper & Row, Publishers, Inc., Medical Department, 2350 Virginia Avenue, Hagerstown, MD (21740), 1972. 125 pages, with 106 illustrations, $17.50.

Beginning with an abbreviated embryologic and anatomic description of the vulva, the text, which might more appropriately be called an atlas, then proceeds in a concise and logical fashion to describe the common and esoteric pathologic changes that can occur in this accessible anatomic area.

Vulvar dermatoses, a multifaceted problem to both the gynecologist and dermatologist, receive comprehensive coverage. Except for the section devoted to herpes progenitalis the natural history of pyogenic and venereal vulvar disease is succinctly presented with specific recommendations as to medical and surgical treatment for each entity. I was frustrated by the brief and classic approach taken by the authors in their material on vulvar herpes. There is great interest today in herpes virus Type II and its, at present, tenuous link with gynecologic malignancy. In addition, new effective though somewhat controversial therapies are now available to shorten the course of the frustrating ulcerative herpetic lesion. Neither factor is at all explored in the authors' discussion of herpes progenitalis and I feel they should be included even in a monograph of this size.

The chapter on benign and malignant vulvar tumors preceded by a unique section on "tumorlike" conditions is excellent. A wealth of statistical and therapeutic information, including a very up-to-date clinical staging of vulvar carcinoma, is contained within what might be considered a short chapter to cover this important topic.

In any evaluation of a text of vulvar disease it is on the discussion of so-called "white lesions" of the vulva that attention is always focused. This is logical for terms such as leukoplakia, kraurosis and lichen sclerosis et etrophicus conjure confusion in the minds of residents-in-training and seasoned clinicians alike. The authors have approached this subject by presenting their own classification of dysplastic and premalignant vulvar lesions. As with many personal schemes, this may function well for them but I believe adds little to our true understanding of these entities especially when nonhelpful terms such as "melanosis circumscripta praeblastomatosa of Dubrevilh (lentigo maligna)" are included in the classification.

The authors have compiled an impressive series of color gross and microscopic photographs to illustrate the many lesions they describe and these are adequately captioned. A fine bibliography and complete index enhance the book's usefulness.

In summary I believe this new text on vulvar disease has a broad appeal not only to those in residency training but also to all clinicians within the speciality of gynecology and in general practice who, I'm sure, are often faced with a myriad of vulvar pathologies. *Diseases of the Vulva* is a well planned comprehensive effort and certainly a credit to its authors.

MOREY FILLER, MD

* * *

THE JACK SPRAT COOKBOOK—Or Good Eating on a Low-Cholesterol Diet—Polly Zane; foreword by Campbell Moses, MD, Medical Director of the American Heart Association. Harper & Row, Publishers, Inc., 10 East 53rd Street, New York City (10022), 1973. 497 pages, $10.95.

Polly Zane's husband was recovering from a heart attack. She was then told that her whole family had to change its nutritional way of life. In her own words, " . . . I could have cried. Here suddenly, and with no warning to brace myself, I was being told to forget not only most of the foods my family enjoyed but also a large number of my cooking methods. And not next month or next week but right away. *Starting Now.*"

It was hard work finding out how to do this. Although she did find a lot of information on low-cholesterol, low-saturated fat diet, " . . . the recipes varied in reliability but seldom in dullness. And while my husband had a strong motivation to stay with the diet, unappetizing though it might have been, he wasn't the only one concerned. The food I cooked had to be eaten by everybody in the family. Available information simply did not supply enjoyable meals. There had to be a better way."

Polly Zane found a better way. She describes the process as one of trial and error, but it was also, obviously, a labor of love. The results are embodied in this attractive cookbook whose special appeal is that it is written by someone who has really been there.

This book is a collection of recipes to chose from at random. It is intended for anyone, including the heart patient, who wishes to keep his blood cholesterol level down. The recipes produce dishes which are medically acceptable and look as if they would be a pleasure to eat. Many old favorites are revamped in healthy trappings which take them off the banned list and restore them to the table.

This is a real do-it-yourself book and is to be recommended.

IAN CARR, MD

PATHOLOGY OF THE CEREBRAL BLOOD VESSELS—William E. Stehbens, MD, D Phil, FRC Path, FRCPA, MRACP, Professor of Pathology, Albany Medical College of Union University, and Director of the Electron Microscopy Unit, Veterans Administration Hospital, Albany, New York. The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Mo. (63141), 1972. 661 pages, with 322 illustrations, $44.50.

This book is an excellent compilation of much material, arranged in rather orthodox fashion. The first two chapters on normal and abnormal variations of cerebral blood vessels present a huge amount of statistical information, a welcome source of reference. This compilation of existing material in the literature is Dr. Stehbens' strongest point. However, the reader may at times wish for a more critical analysis of these data, their sources, or the reasons for the variations in the cited statistics. Following a conventional presentation of atherosclerosis and thrombosis, embolism, infarction, and vascular insufficiency are four chapter divided classically into extradural, subdural, subarachnoid and intercerebral hemorrhage. An etiological or pathogenetic presentation would have been preferable to this reviewer.

The variation in emphasis and space allotted to certain subjects is a more serious objection. Cerebral aneurysms are discussed exhaustively, as are subclavian steal syndrome, bruit, and the gross anatomical appearance, variation, and location of primary hypertensive intracerebral hemorrhages. Recent areas of investigation and interest, such as cerebral edema, the perivascular space, diabetes mellitus, or the changes seen with aging are relatively slighted. Lupus erythematosus, amyloid microangiopathy or the effects of x-rays on cerebral vessels are each allotted one quarter of one page or less. Also surprising is the omission of electron microscopic illustration or any discussion of ultrastructural changes by an author listed as director of the Electron Microscopy Unit.

The book is a comprehensive and valuable compilation of the gross changes seen in common diseases of the cerebral blood vessels as described in the literature. The references are extensive, and the illustrations are clear, and of good quality, albeit conventional.

URSULA T. SLAGER, MD

* * *

VESICOURETERAL REFLUX AND PYELONEPHRITIS—John A. Hutch, MD, Associate Clinical Professor of Urology, University of California, San Francisco; and Arjan D. Amar, MB, MS, FRCS(c), FACS, Assistant Clinical Professor of Urology, University of California, San Francisco, Chief, Department of Urology, Kaiser-Permanente Medical Center, Walnut Creek, California. Appleton-Century-Crofts, Educational Division, Meredith Corporation, 440 Park Avenue South, New York City (10016), 1972. 236 pages, $12.75.

This volume represents the final monograph to be published by the late John A. Hutch. His untimely demise has deprived urology and medicine in general of an original thinker and a careful investigator. This monograph is a collaborative effort of both Dr. Hutch and Dr. Amar, a clinician who is known to be quite innovative. Much of the previous work of these two men is summarized in this volume.

The illustrations are by and large excellent. The first three chapters covering the historical aspects of the subjects, anatomic and physiologic considerations, and diagnosis are quite thorough. The chapter on surgical techniques covers the authors' approaches well but one might wish that this section was expanded for completeness, as a number of widely used techniques are omitted.

The remaining two sections are somewhat dogmatic and represent a relatively aggressive approach to the problem. This does not really detract from the overall work for the authors are certainly entitled to their opinions and their rationale is well-presented.

The style is most readable and lucid. This volume is highly recommended for urologic residents and urologists with a minor interest in the problem. For those dealing extensively with the problem much of this material will be "old hat" but enjoyably presented. I would also recommend this volume to those pediatricians, internists, and radiologists who feel that surgery has virtually no place in the treatment of this disease.

GEORGE W. KAPLAN, MD

* * *

HERITABLE DISORDERS OF CONNECTIVE TISSUE—Fourth Edition—Victor A. McKusick, MD, Professor of Medicine, The Johns Hopkins University School of Medicine and Physician, The Johns Hopkins Hospital, Baltimore. The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, MO (63141), 1972. 878 pages, $32.50.

The fourth edition of this important work is well written and organized, authoritative and complete. The opening two chapters deal first with the terminology, classification, and concepts of medical genetics and secondly with an introduction to the biology of normal connective tissue. The former in particular is concise and understandable to those not immediately in the field of medical genetics. The subsequent 11 chapters document in meticulous detail the clinical, pathophysiologic, and genetic aspects of disorders such as the Marfan's syndrome, the Ehlers Danlos syndrome, osteogenesis imperfecta, the various mucopolysaccharidoses, alkaptonuria, pseudoxanthoma elasticum and a host of others. Although McKusick specifically states the book is directed most particularly to the generalist, internist and pediatrician without particular subspecialization, the wealth of detail and the profusion of pictorial illustrations make this work, of course, of deep interest to the specialist in virtually every area of medicine. A major objective, well achieved, is the synthesis and documentation in one place, of information about these diverse and often rather rare conditions. The bibliographical references are voluminous; the indexing is somewhat scanty. The book is dedicated to Garrod and "all who believe, as he did, that the clinical investigation of hereditary disorders can shed light on normal developmental and biochemical mechanisms." It is a welcome addition to the library of all those who subscribe to this belief.

WILLIAM N. VALENTINE, MD

* * *

NEONATAL HEART DISEASE—Edited by William F. Friedman, MD, Chief, Division of Pediatric Cardiology, Associate Professor of Pediatrics and Medicine, University of California, San Diego, School of Medicine; Michael Lesch, MD, Department of Medicine, Harvard Medical School; and Edmund H. Sonnenblick, MD, Director of Cardiovascular Research, Harvard Medical School. Grune & Stratton, Inc., 111 Fifth Avenue, New York City (10003), 1973. 299 pages, $18.50.

This book is a compilation of articles originally published in the July, September, and November, 1972 and January, 1973 issues of *Progress in Cardiovascular Disease*. The articles and authors are outstanding. It should be pointed out that the chapters deal with more than just "Neonatal Heart Disease," and therefore the title of the book is misleading. Likewise, much of the work had been reported previously in other original articles by the various authors. Thus, I feel that this book contains relatively little new information not already present in the medical literature.

FORREST ADAMS, MD

in memoriam

Arnot, Philip H., San Francisco. Died January 25, 1974 in San Francisco, aged 79. Graduate of the University of California Medical School, Berkeley-San Francisco, 1920. Licensed in California in 1920. Doctor Arnot was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Burket, Joseph Arthur, Saratoga. Died January 27, 1974 in Los Gatos, aged 59. Graduate of the University of Louisville School of Medicine, 1939. Licensed in California in 1945. Doctor Burket was a member of the Santa Clara County Medical Society.

Conry, Robert Francis, San Leandro. Died January 19, 1974, aged 60. Graduate of the University of Nebraska College of Medicine, Omaha, 1944. Licensed in California in 1949. Doctor Conry was a member of the Alameda-Contra Costa Medical Association.

Cunningham, James Emery, San Bernardino. Died February 10, 1974 in San Bernardino, aged 53. Graduate of the University of Southern California School of Medicine, Los Angeles, 1949. Licensed in California in 1949. Doctor Cunningham was a member of the Santa Barbara County Medical Society.

Cushman, Glenn F., San Francisco. Died in San Francisco February 16, 1974, aged 73. Graduate of the University of Oregon Medical School, Portland, 1925. Licensed in California in 1925. Dr. Cushman was a retired member of the San Francisco Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Ellis, Grant, Napa. Died February 12, 1974 in Napa of heart disease, aged 70. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1931. Licensed in California in 1932. Doctor Ellis was an associate member of the Alameda-Contra Costa Medical Association.

Hall, Cameron B., Los Angeles. Died January 20, 1974 in Los Angeles, aged 57. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1944. Licensed in California in 1944. Doctor Hall was a member of the Los Angeles County Medical Association.

Hoag, Harry James, sr., San Jose. Died February 6, 1974 in San Jose, aged 91. Graduate of the University of Illinois College of Medicine, Chicago, 1905. Licensed in California in 1923. Doctor Hoag was a retired member of the Santa Clara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Holmes, Olin Monroe, Lacey, San Juan Islands, Washington, and San Mateo. Died February 9, 1974 in San Mateo, aged 78. Graduate of the University of California Medical School, Berkeley-San Francisco, 1927. Licensed in California, 1927. Doctor Holmes was a retired member of the San Mateo County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Howard, Lot D., jr., San Francisco and Carmel. Died February 25, 1974 in Carmel of metastatic bronchiogenic carcinoma, aged 65. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1934. Licensed in California in 1934. Doctor Howard was a member of the San Francisco Medical Society.

Koefod, Hilmar Olaf, Santa Barbara. Died February 12, 1974 in Santa Barbara, aged 86. Graduate of Harvard Medical School, Boston, 1916. Licensed in California in 1918. Doctor Koefod was a retired member of the Santa Barbara County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

Korostoff, Bernard, Pacoima. Died January 3, 1974 in Northridge of cancer, aged 65. Graduate of the University of Maryland School of Medicine, Baltimore, 1932. Licensed in California in 1946. Doctor Korostoff was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Krugmeier, Carl E., Costa Mesa. Died September 22, 1973 in Costa Mesa of myocardial infarction, aged 80. Graduate of Chicago College of Medicine and Surgery, 1917. Licensed in California in 1920. Doctor Krugmeier was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Latini, John Julio, Los Altos. Died February 21, 1974 in Mountain View of heart disease, aged 50. Graduate of Des Moines Still College of Osteopathy, Iowa, 1953. Licensed in California in 1956. M.D. degree from California College of Medicine, University of California, Irvine, 1962. Doctor Latini was a member of the Santa Clara Medical Society.

Lenahan, George T., San Francisco. Died February 15, 1974, aged 68. Graduate of Creighton University School of Medicine, Omaha, 1930. Licensed in California in 1930. Doctor Lenahan was a member of the San Francisco Medical Society.

Ross, Peter, Richmond. Died January 22, 1974 in San Pablo of carcinoma of the colon, aged 75. Graduate of Johan Wolfgang Goethe-Universität Medizinische Fakultät, Frankfurt, 1923. Licensed in California in 1934. Doctor Ross was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Scott, Walter, Hollywood. Died January 25, 1974 in Palm Springs of cancer, aged 69. Graduate of University of Michigan Medical School, Ann Arbor, 1930. Licensed in California in 1938. Doctor Scott was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Wiper, Thomas Benedict, Burlingame. Died January 31, 1974 in Kentfield, aged 70. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1931. Licensed in California in 1931. Doctor Wiper was a member of the San Francisco Medical Society.

Integument!

Our skin—the human integument—covers us, defines us, protects us. But skin is subject to cuts, burns, abrasions. And infections. Neosporin Ointment fights infection by providing broad antibacterial action against susceptible skin invaders. It contains antibiotics that are rarely used systemically, reducing the risk of sensitization.

INDICATIONS: *Therapeutically*, used as an adjunct to appropriate systemic therapy for topical infections, primary or secondary, due to susceptible organisms, as in: • infected burns, skin grafts, surgical incisions, otitis externa • primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis) • traumatic lesions, inflamed or suppurating as a result of bacterial infection.

Prophylactically, the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing.

CONTRAINDICATIONS: Not for use in the external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of the components.

PRECAUTION: As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms and/or fungi. Appropriate measures should be taken if this occurs. Articles in the current medical literature indicate an increase in the prevalence of persons allergic to neomycin. The possibility of such a reaction should be borne in mind.

Complete literature available on request from Professional Services Dept. PML.

NEOSPORIN® Ointment

(POLYMYXIN B-BACITRACIN-NEOMYCIN)

Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5,000 units; zinc bacitracin 400 units; neomycin sulfate 5 mg. (equivalent to 3.5 mg. neomycin base); special white petrolatum q.s. In tubes of 1 oz. and ½ oz. and 1/32 oz. (approx.) foil packets.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

At Your Service in The Golden State

In the region named *California* by Spanish adventurers probably after the name of a treasure island in a popular Spanish tale . . .

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY, MISSOURI 64137

is represented by . . .

Dick Bastin

Vito Bell

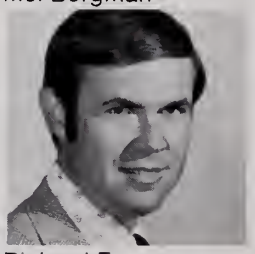
Mel Bergman

Barry Bialkoski

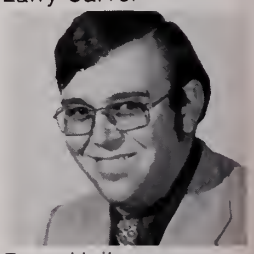
Larry Carver

Dave Evans

Bob Fatch


Richard Foss

Dave Hawks

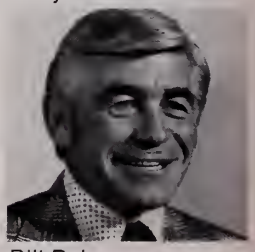

Barry Heilman

Bob Jones

Randy Kennick

Ruth MacKie

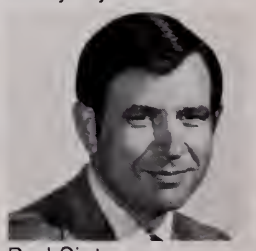
Marty Myers


Bill Palmer

John Patella

Jim Petric

Mike Ryan


Bud Sinkey

Ernie Smith

Bill Stauch

Lorin Waxman

Frank Yannarell

These representatives bring you . . . . . .

Puts comfort in your prescription for nicotinic acid

Description Each capsule contains 400 mg of nicotinic acid in a special base that provides a prolonged systemic effect
Indications NICO-400® is recommended for all disease states in which nicotinic acid has been used These include conditions associated with deficient circulation and for use in the correction of nicotinic acid deficiencies
Contraindications Individuals with a hypersensitivity to nicotinic acid, severe hypotension or hemorrhaging
Warnings Use with caution in those patients with history of peptic ulcer severe diabetes impaired gall bladder or liver functions and in pregnant women
Adverse Reactions Patients should be informed of the short lived reactions experienced with nicotinic acid therapy cutaneous flushing a sensation of warmth tingling and itching of the skin increased gastrointestinal motility and sebaceous gland activity
Dosage and Administration One capsule every 12 hours or as directed by physician
Caution Federal law prohibits dispensing without prescription
How Supplied Bottles of 100 capsules

Another patient benefit product from
MARION PHARMACEUTICAL DIVISION
MARION LABORATORIES INC

THE OPTIMAL DOSE, 400-mg, timed-release NICO-400® (nicotinic acid) capsule provides

- Controlled flushing for the desired effects without therapy-limiting side effects.
- Convenient b.i.d. dosage that's less likely to be forgotten.
- The economy of nicotinic acid medication.

For comfort wherever nicotinic acid is used

NICO-400®

(nicotinic acid) Plateau CAPS®

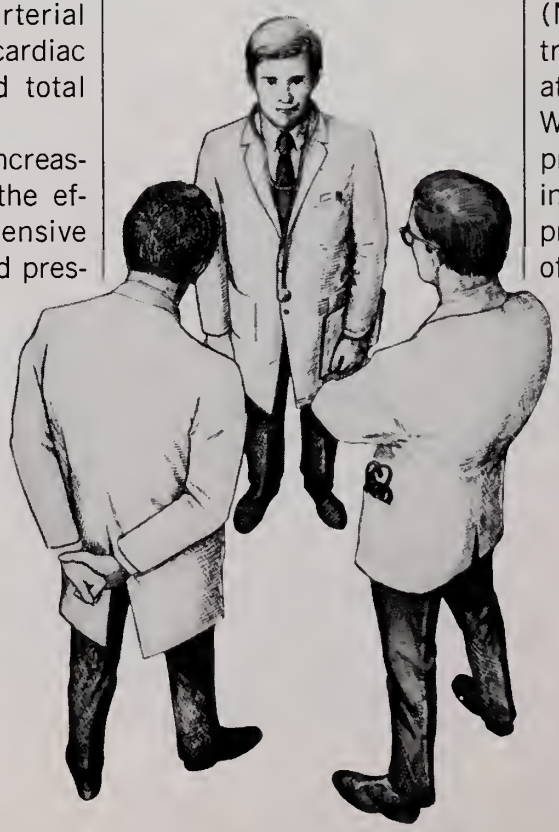
The more physicians consider the hemodynamics of lowering blood pressure...

Most physicians now agree on the importance of reducing blood pressure in the hypertensive patient. But high blood pressure exists, of course, only as part of a complete clinical picture. The hemodynamic profile of well-established essential hypertension is characterized by elevated arterial blood pressure, normal cardiac output, and increased total peripheral resistance.

And so, physicians are increasingly concerned with the effects of an antihypertensive agent not only on blood pressure itself but also on the hemodynamic pattern—in short, with the total effect of the drug. *Does* it indeed help lower blood pressure effectively? *Is* peripheral resistance reduced? *Are* cardiac output and renal functions maintained? And, also, is there likely to be drug-induced postural hypotension serious enough to pose a threat to the patient's cerebrovascular status?

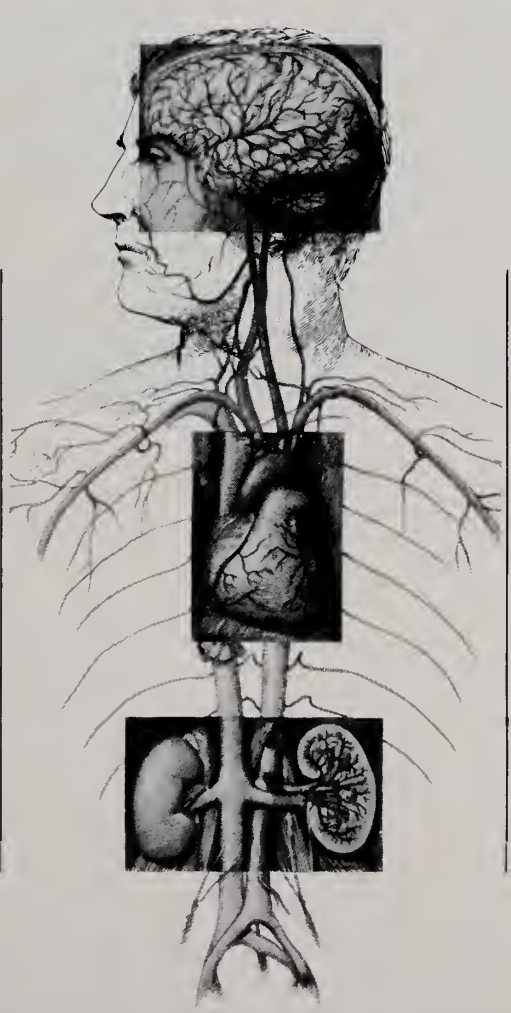
With this emphasis on overall drug performance has come a growing reliance on ALDOMET® (Methyldopa, MSD) in the treatment of sustained moderate hypertension.

With its unique hemodynamic profile, ALDOMET has drawn increasing attention and approval from physicians. First, of course, for its efficacy in



the more physicians rely on this unique antihypertensive

lowering blood pressure. But there are other considerations as well. Cardiac output is usually maintained with no cardiac acceleration; in some patients the heart rate is actually slowed. Peripheral resistance is apparently reduced. ALDOMET does not usually compromise existing renal function; it generally does not reduce renal blood flow, glomerular filtration rate, or filtration fraction. And ALDOMET usually does not cause symptomatic postural or exercise hypotension.



Some patients on continuous methyldopa therapy may develop a positive direct Coombs test. For more details, see the brief summary of prescribing information.

Contraindicated in active hepatic disease and known sensitivity to the drug. Not recommended in pheochromocytoma or pregnancy. It should be used with caution in patients with a history of liver disease or dysfunction. Discontinue the drug if fever, abnormal liver function, jaundice, or acquired hemolytic anemia occurs.

In most cases of sustained moderate hypertension

TABLETS, 250 mg

ALDOMET®

(METHYLDOPA | MSD)

smoothly lowers blood pressure

For a brief summary of prescribing information, please see following page.

In most cases of sustained moderate hypertension

TABLETS, 250 mg

ALDOMET®
(METHYLDOPA | MSD)

smoothly lowers blood pressure

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; known sensitivity. Not recommended in pheochromocytoma. Unsuitable in mild or labile hypertension responsive to mild sedation or thiazide therapy. Use cautiously in patients with history of previous liver disease or dysfunction.

Warnings: Acquired hemolytic anemia has occurred rarely in association with therapy with methyldopa. Should clinical symptoms indicate the possibility of anemia, hemoglobin and/or hematocrit determinations should be performed. If anemia is present, appropriate laboratory studies should be done to determine if hemolysis is present. Evidence of hemolytic anemia is an indication for discontinuation of the drug. Discontinuation of methyldopa alone or the initiation of adrenocortical steroids usually results in a prompt remission of the anemia. Rarely, however, fatalities have occurred.

Some patients on continued therapy with methyldopa develop a positive direct Coombs test; incidence reported has averaged between 10% and 20%. It rarely occurs in first six months of therapy, and if not seen within twelve months, is unlikely to develop with continued administration. Positive Coombs test is dose-related; lowest incidence occurs in patients on 1 g methyldopa or less per day. Reversal of the positive Coombs test occurs within weeks to months after discontinuation of methyldopa. Prior knowledge of a positive Coombs reaction aids in evaluation of cross match for transfusions. Patients with positive Coombs tests at time of cross match may exhibit incompatible minor cross match. When this occurs, an indirect Coombs test should be performed. If negative, transfusion with blood otherwise compatible in the major cross match may be carried out. If positive, advisability of transfusion with blood compatible in major cross match should be determined by hematologist or expert in transfusion problems.

Fever has occurred within first three weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first two to three months of therapy. Rare cases of fatal hepatic necrosis have been reported. Liver biopsy in several patients with liver dysfunction has shown microscopic focal necrosis compatible with drug hypersensitivity. Rarely, reversible reduction in leukocyte count with primary effect on granulocytes has been seen; reversible agranulocytosis has been reported. Methyldopa may interfere with measurement of creatinine by alkaline picrate method and of uric acid by phosphotungstate method. When used with other antihypertensive drugs, potentiation of antihypertensive action may occur.

Usage in Pregnancy and Childbearing Age—Not recommended in pregnancy. In women of childbearing age, weigh potential benefits against possible fetal hazards.

Precautions: Perform periodic hepatic function tests and white cell and differential blood counts during first six to twelve weeks of therapy or in unexplained fever. Discontinue if fever, abnormalities in liver function tests, or jaundice appears. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, spuriously high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. Discontinue drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Anesthetics requirements may be reduced; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension may occur after dialysis because methyldopa is removed by this procedure.

Dosage should be limited initially to 500 mg daily when following previous antihypertensive agents other than thiazides. Do not exceed recommended daily dose of 3.0 g. Patients with impaired renal function may respond to smaller doses than patients with normal kidney function. Syncope in older patients has been related to increased sensitivity in those with advanced arteriosclerotic vascular disease; this may be avoided by lower doses. Tolerance occasionally seen either early or late, but more likely between second and third month after initiation of therapy; increased dosage or combined therapy with a thiazide frequently restores effective control.

Adverse Reactions: Sedation, usually transient, may be seen during initial therapy or when dosage is increased. Headache, asthenia, or weakness may be noted as early, transient symptoms. Symptoms associated with effective lowering of blood pressure, including dizziness, lightheadedness, and symptoms of cerebrovascular insufficiency, are seen occasionally. Angina pectoris may be aggravated. Symptoms of orthostatic and exercise hypotension may occur; if symptoms occur, reduce dosage. Bradycardia, nasal stuffiness, mild dryness of mouth, and gastrointestinal symptoms including distension, constipation, flatus, and diarrhea occur occasionally; these can be relieved by reducing dosage. Nausea and vomiting have been reported in only a few patients. Sore tongue or "black tongue," pancreatitis, and inflammation of salivary glands may occur.

Weight gain and edema occur infrequently; if edema progresses or signs of pulmonary congestion appear, discontinue drug. Rarely, urine exposed to air may darken due to breakdown of methyldopa or its metabolites. Other rare reactions include breast enlargement, lactation, impotence, decreased libido, skin rash, mild arthralgia, myalgia, paresthesias, parkinsonism, psychic disturbances including nightmares, reversible mild psychoses or depression, reversible thrombocytopenia, drug-related fever and abnormal liver function studies with jaundice and hepatocellular damage (see **Warnings** and **Precautions**), rise in BUN, and a single case of bilateral Bell's palsy.

Supplied: Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

MSD
MERCK SHARP & DOHME

ADDENDUM

Let's make blood pressure "required reading" for all physicians.

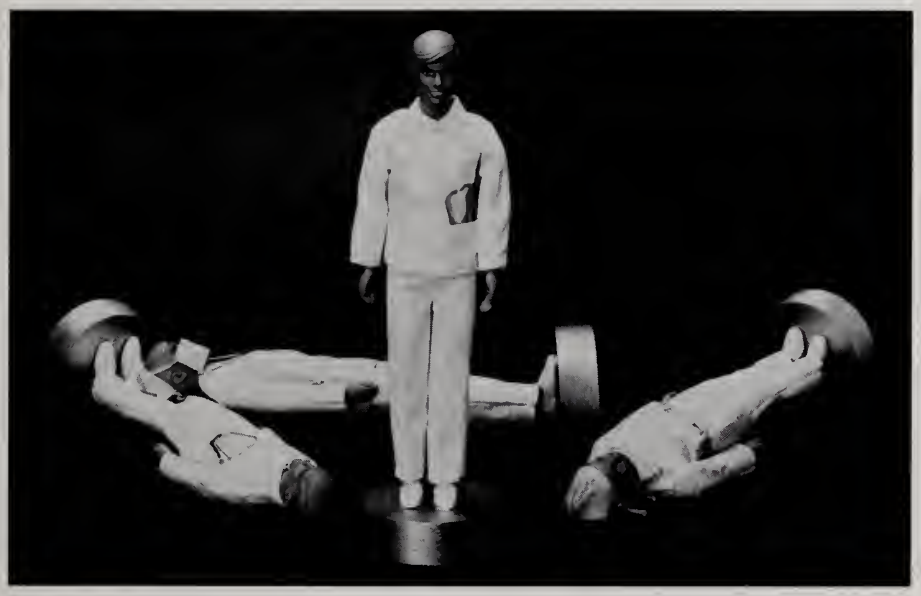
With recent estimates that about 23 million Americans have high blood pressure—and that half of them are not even aware of it—detection of the problem in asymptomatic persons has become an issue of national importance.

Family physicians are being urged to take blood pressure readings as a matter of office routine, regardless of the presenting complaint or the reason for the visit. And because many people do not see a family physician for relatively long periods of time, some experts are suggesting that ophthalmologists, gynecologists, dermatologists, orthopedists, psychiatrists, dentists, school nurses, family planning counselors, and other health-care personnel make blood pressure reading a routine part of every examination or consultation.

Of course, a diagnosis of hypertension cannot be made on the basis of a single reading, but routine blood pressure readings can uncover potential trouble in a certain proportion of patients. And when trouble is suggested, further evaluation can be pursued more effectively.

Blood pressure—"required reading" for all physicians.

The malpractice menace: It strikes 3 out of 4 doctors.



That's right. Three out of four doctors get hit with a malpractice suit during their medical careers.

It can happen anytime. And to any doctor at any stage of his professional life.

That's why no doctor can afford to ignore the malpractice menace. Not only because the financial losses can be shattering. But also because the stigma attached to a malpractice action can be so damaging.

Now there's a survival kit

Medical Economics has a special survival kit to help you with this problem. It's our cassette series on "Malpractice: What you must know and do."

With this series, you get 10 one-hour cassettes that are loaded with advice from the finest medico-legal minds, insurance and medical experts, plus defendant and plaintiff attorneys.

A series just for you

This series is designed especially for busy doctors like yourself. All it takes is a press of the button and you can listen anywhere (in your car, in your office, or at home) to what experts feel you must know and do about the malpractice menace.

Each cassette is an *exclusive and personal* presentation, too. These *are not* our magazine articles recorded on tape. And *not* something taken from lectures or extracts of meetings.

You'll listen and learn what you must know about current malpractice law to avoid suit, how to guard against liability for the acts of others, techniques to obtain informed consent that stands up in court, what to do (and not to do) if you're sued. Plus many more things to help protect your practice and resources from a malpractice action.

$75 for the package

And you can't beat the price, either. You pay only $75. And you get 10 cassettes packaged in a handsome album filled with practical, on-target advice.

Just complete the coupon below. Order your survival kit and learn how to protect yourself against the malpractice menace.

Medical Economics Cassette Service
Oradell, New Jersey 07649

Tell me what I must know and do to protect myself against the malpractice menace.

☐ Bill me $75 for your 10 cassette series.
☐ Also, send a Panasonic Recorder/Player and bill me $44.95.
☐ Send me information on your other cassette services.

Name _____

Address _____

City _____ State _____ Zip _____

Medical Specialty _____

Physicians who use Safeguard's medical billing system improve cash flow up to 30%

Safeguard
BUSINESS SYSTEMS INC.
6117 Malt Avenue, Los Angeles, Ca 90040

PROLOID® (thyroglobulin)

Caution: Federal law prohibits dispensing without prescription.

Description. Proloid (thyroglobulin) is obtained from a purified extract of frozen hog thyroid. It contains the known calorigenically active components, Sodium Levothyroxine (T_4) and Sodium Liothyronine (T_3). Proloid (thyroglobulin) conforms to the primary USP specifications for desiccated thyroid—for iodine based on chemical assay—and is also biologically assayed and standardized in animals.

Chromatographic analysis to standardize the Sodium Levothyroxine and Sodium Liothyronine content of Proloid (thyroglobulin) is routinely employed.

The ratio of T_4 and T_3 in Proloid (thyroglobulin is approximately 2.5 to 1.

Proloid (thyroglobulin) is stable when stored at usual room temperature.

Indications. Proloid (thyroglobulin) is thyroid replacement therapy for conditions of inadequate endogenous thyroid production: e.g., cretinism and myxedema. Replacement therapy will be effective only in manifestations of hypothyroidism.

In simple (nontoxic) goiter, Proloid (thyroglobulin) may be tried therapeutically, in nonemergency situations, in an attempt to reduce the size of such goiters.

Contraindication. Thyroid preparations are contraindicated in the presence of uncorrected adrenal insufficiency.

Warnings. Thyroglobulin should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 0.5 to 1.0 grain (32 to 64 mg) and increased by the same amount in increments at two-week intervals. This demands careful clinical judgment.

Morphologic hypogonadism and nephroses should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.

Myxedematous patients are very sensitive to thyroid and dosage should be started at a very low level and increased gradually.

Precaution. As with all thyroid preparations this drug will alter results of thyroid function tests.

Adverse Reactions. Overdosage or too rapid increase in dosage may result in signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.

Dosage and Administration. Optimal dosage is usually determined by the patient's clinical response. Confirmatory tests include BMR, T_3 ^{131}I resin sponge uptake, T_3 ^{131}I red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Clinical experience has shown that a normal PBI (3.5-8 mcg/100 ml) will be obtained in patients made clinically euthyroid when the content of T_4 and T_3 is adequate. Dosage should be started in small amounts and increased gradually with increments at intervals of one to two weeks. Usual maintenance dose is 0.5 to 3.0 grains (32 to 190 mg) daily.

Overdosage Symptoms. Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

(Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)

How Supplied. ¼ grain; ½ grain; scored 1 grain; 1½ grain; scored 2 grain; 3 grain; and scored 5 grain tablets, in bottles of 100 and 1000.

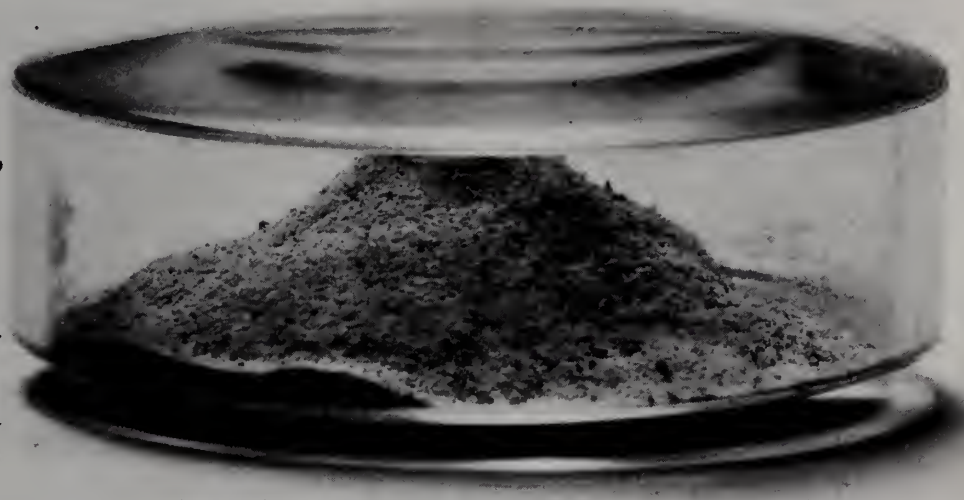
Full information available on request.

WARNER/CHILCOTT
Division, Warner-Lambert Company
Morris Plains, New Jersey 07950

PR-GP-31-B/W

IN NATURAL THYROID THERAPY:

ARE PATIENTS GETTING THE POTENCY YOU PRESCRIBE?



Unlike U.S.P. desiccated thyroid, Proloid®(thyroglobulin) offers the assurance of constant potency.

To begin with, Proloid is uniquely purified. The thyroglobulin extracted from hog thyroid is devoid of any glandular debris.

Then, Proloid is chemically and biologically assayed to assure consistent metabolic activity from batch to batch. The T_4 and T_3 content of every dose is blended for optimal thyroid replacement.

Important, too, is the fact that Proloid is invariably "fresh" when your patients take it. Under proper storage conditions, its potency will not diminish for at least four years.

All of which adds up to this: the potency of Proloid is constant...for more consistent results.

PROLOID®
(thyroglobulin)

natural thyroid therapy that leaves nothing to chance

situation:

Impaired cardiac status . . . straining at stool may be hazardous. . .

constipation:

Restricted physical activity . . . often, major changes in customary daily routine . . . constipating medications. . .

laxation:

SENOKOT Tablets or Granules, taken at bedtime, generally induce effective, yet comfortable evacuation in the morning . . . help avoid straining.

Supplied: SENOKOT Tablets (small, easy-to-swallow) — Bottles of 50 and 100. SENOKOT Granules (delicious, cocoa-flavored) — 4, 8 and 16 ounce (1 lb.) canisters.

Senokot Tablets Granules

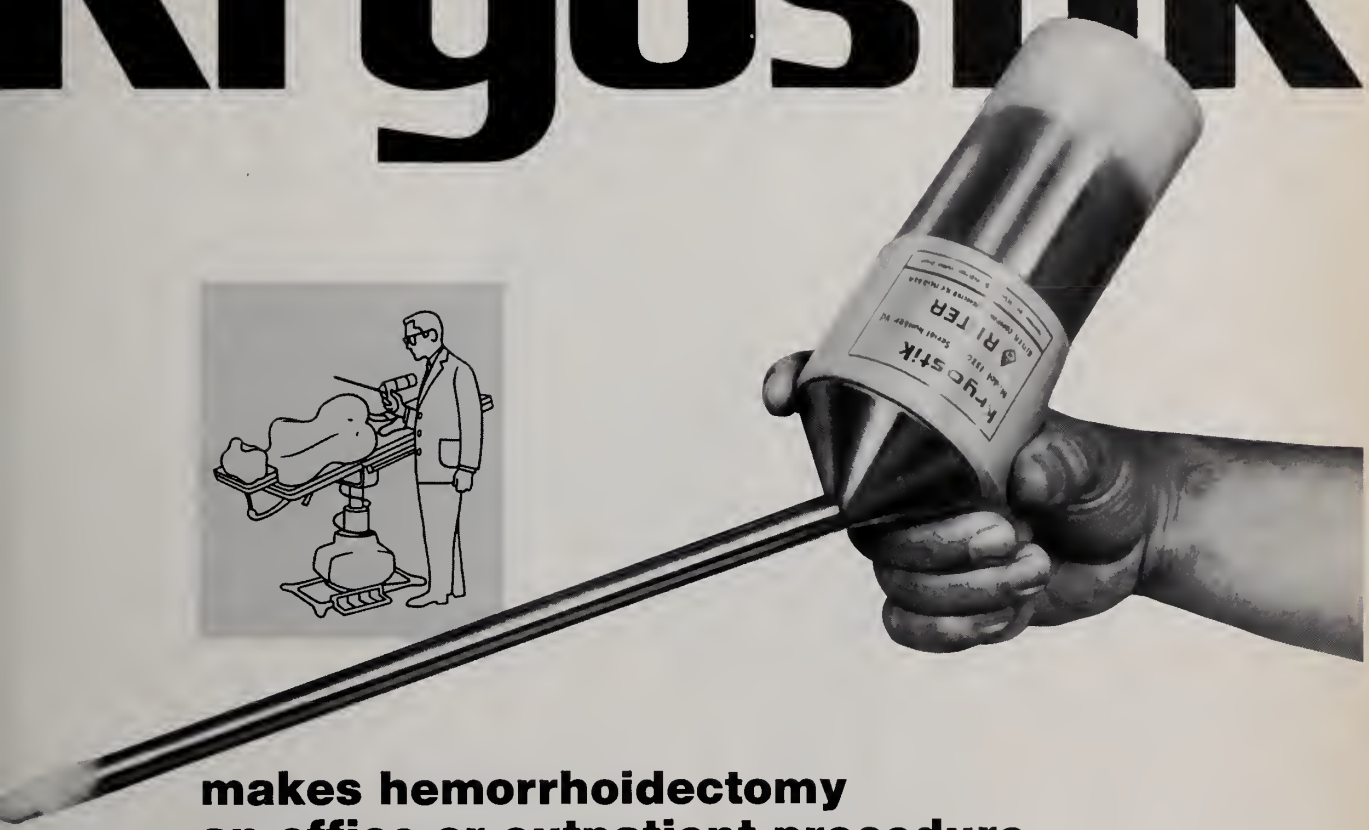
(standardized senna concentrate)

a natural laxative

PURDUE FREDERICK

© 1974, THE PURDUE FREDERICK COMPANY
NORWALK, CONN 06856 136874

Kryostik™



makes hemorrhoidectomy an office or outpatient procedure.

Imagine performing hemorrhoidectomies in your office or outpatient department . . . and sending the patient home to resume his normal activities the same day! It's possible with Kryostik—the first cryo-surgical instrument designed *specifically* for hemorrhoidectomies, as an alternative or adjunct to your present procedure.

A temperature of −196°C produces almost immediate anesthesia in the treatment area. As hemorrhoidal tissues rapidly freeze, the temperature of adjacent tissue rises. When the Kryostik is removed, hemorrhoidal tissues thaw rapidly. Their individual cells die and liquify. Unfrozen adjacent tissue remains soft and pliable, so post-operative pain is negligible; bowel function can be performed without pain or difficulty; and post-operative care is minimal.

The Kryostik is completely portable and weighs less than 2 pounds. It is effective on internal and external hemorrhoids . . . providing a means to treat hemorrhoid patients quickly and simply.

Ask your Authorized Ritter Dealer about Kryostik, or send for full-color brochure containing complete details.

RITTER
SYBRON CORPORATION
ROCHESTER, N Y 14603

Now available in California!

Please send me complete details on the Kryostik Surgical Instrument.

Ritter Company
Box 848
Rochester, N.Y. 14603

Name

Address

City State Zip

Leonardo could have qualified for AMWA membership.

Can you?

The great Renaissance man could have made it on the strength of his medical writing alone.

Or as an illustrator.

Or simply as a medical scientist.

But you can earn membership in the American Medical Writers Association—AMWA— by being any one of these. As well as by being an editor, librarian, clinician, medical photographer...or practically anything *else* connected with medical communications.

The one *in*flexible criterion: you must share the conviction of AMWA's current 1,500 members that clear, concise communications is a vitally important art to be cultivated and refined.

To achieve that end, AMWA conducts workshop sessions in a variety of specialized facets of communications —including explorations into the latest media. It holds local, regional and national meetings that enable editors, physicians, film-makers, writers, publishers, illustrators and a wide spectrum of scientific communicators to meet, talk, learn to understand one another's problems better. And it publishes a journal that exists for one purpose only: to encourage and nurture concise, lucid medical communications.

To learn more about how to join the rapidly growing ranks of AMWA members who share your concerns, write to the Executive Secretary, American Medical Writers Association, 9650 Rockville Pike, Bethesda, Maryland 20014.

Just because DaVinci missed out on AMWA membership is no reason you should.

AMERICAN MEDICAL WRITERS ASSOCIATION

(Continued from Page 30)

OFFICES FOR LEASE OR RENT

EUREKA—MEDICAL SUITE AVAILABLE. 1,000 to 1,300 square feet depending on need. New Professional Building adjacent to hospital. Lease available with purchase option. Excellent outdoor recreation area. Hunting, fishing, boating, hiking—you name it. Come and relax on the North Coast, (707) 443-3005.

ESCONDIDO, CALIFORNIA—New medical suite, 1,872 sq. ft.—suitable for Internist, Generalist or Orthopod.—one or two physicians—near hospital. Fast growing area; call (714) 747-8430.

OFFICE FOR RENT: 2,109 sq. ft. Ideal location, center of town, across the street from large hospital. Ophthalmology suite or will partition to suit any medical practice. Write or phone Dr. Mario R. Galliano, 204 West College Street, Covina, California 91723, (213) 332-7112.

SOUTHERN CALIFORNIA, LAGUNA NIGUEL—A rapidly growing area. 30,000 sq. ft. Medical Center Complex minutes from beach and equal distance from three (3) hospitals with OB-GYNS, Surgeons, Ophthalmologist, Pediatrician, General Practitioner: Need Internists, G.P. sub-specialties of Int. Medicine, ENT, Orthopedic Surgeon and Urologist. Please call for information (714) 495-4601.

SOUTHERN CALIFORNIA, EL TORO, Medical-Dental Building, now leasing with occupancy August 1974. Ideal location for family oriented practice. Centrally located for rapidly growing area. For information call (714) 831-1321.

FULLY EQUIPPED MEDICAL OFFICE—Ready for immediate occupancy, in a fast growing community of Fairfield, California. Please call (707) 425-6216.

LAFAYETTE, CALIFORNIA needs internist, orthopedist, etc. in new medical building, off street parking. Ready for occupancy. Dr. J. H. Sibley, 3511 School St., Lafayette, CA (415) 284-1600.

THE WESTERN Journal of Medicine

CLASSIFIED RATES

(Classified Advertising is payable in advance)

$2.50 PER LINE
(Average six words per line)

FIVE LINE MINIMUM

BOX NUMBERS $1.50 EXTRA

DEADLINE
Ist of Month Preceding Date of Publication

CLASSIFIED DISPLAY

$25 PER COLUMN INCH

OFFICES FOR LEASE OR RENT

FIFTY YEARS PRACTICE, grossing over $200,000 year. Nothing to buy, rent only. Building 3,500 sq. ft., air conditioned, rent $650.00 plus maintenance. Available April 15. Location downtown Calexico. Option to buy. Call (213) 986-9490 before 9 a.m. Great future appreciation of land value.

HAWAIIAN VACATION HOME FOR LEASE

FLY, DON'T DRIVE—HAWAIIAN (Hanalei, Kauai) VACATION beach home for only $750 per month. Old Hawaiian atmosphere, away from crowded beaches. Excellent skin diving, swimming, and beaches. Sleeps 12. Available April 8 to April 27, May 11 to May 31, and after September 8. Weekly rate $200. For details, pictures, and information, write James R. Christiansen, 1216 State Street, Santa Barbara, CA 93101, telephone (805) 962-8141.

MUTUAL FUNDS

MUTUAL FUND PERFORMANCES are easier to understand with the monthly copyrighted FUNDICATOR Performance/Rankings Reports, covering 435 funds, including 130 NO LOADS. Send $6 for 3-month trial. Fundicator Inc., Dept. J-1, Box AA, Denville, N.J. 07834.

PRACTICE FOR SALE

GENERAL PSYCHIATRIST retiring from partnership after 27 years private practice in Pasadena area. Goodwill for sale. Salary guarantee. Remaining partner will assist takeover. For details communicate — Bruce Williamson, MD, 2453 Huntington Drive, San Marino, CA 91108; (213) 795-7246.

PHYSICIAN

El Cerrito Health Services Center

Full time Physician wanted for Ambulatory Care Center. Excellent opportunity for advancement in the County health system and for instituting innovative programs.

SALARY: $2618 to start. Generous Civil Service benefits: Medical and Life insurance, retirement, holidays and vacation time and malpractice insurance. Work schedule: 8 a.m.-4:30 p.m., M-F.

CONTACT: **ALAN GREENBERG, MD**
Medical Director
El Cerrito Health Services
1401 Chestnut Ave.
Long Beach, Calif.
(213) 599-6666 or 775-1161

PHYSICIAN

Internist or qualified general practitioner for in-patient service of 161 bed County hospital. Days, 40 hour week plus some compensated stand-by. Liberal fringe benefits; congenial atmosphere; semi-rural setting; Calif. license and B.N.D.D. permit required. Salary commensurate with training and experience.

Contact: **BRUCE PICKEN, MD**
Medical Director
Los Angeles County-Mira Loma Hospital
44900 No. 60th St., West
Lancaster, CA 93534 (805) 948-8581, ext 312

PHYSICIAN SPECIALIST, MD

Department of Medicine of a university teaching hospital in So. Calif. offers full-time position to Generalist or Internist, to provide primary medical coverage on a Post-trauma Orthopedic Service. Some background and interest in Orthopedics desirable. If Interested, send C.V. to **R. E. BODFISH, MD,** Rancho Los Amigos Hospital, 7601 E. Imperial Highway, Downey, CA 90242. Equal opportunity for qualified women and minority groups.

INTERNIST

Unique opportunity for Certified or Board Eligible Internist, or resident completing training in June 1974, to join group of three physicians in practice of Internal Medicine in Palo Alto. Beautifully decorated and fully equipped office designed for four busy Internists, located within walking distance of Stanford Medical Center. Part time faculty teaching appointment available, depending upon training and interest. Subspecialty interests welcome but practice is primarily general medicine. Cultural and recreational opportunities limitless on San Francisco Peninsula. Salary guaranteed with bonus negotiable on basis of production. Opportunity available to join Corporation within one or two years if mutually satisfactory.

Write or phone **Spiegl - St. Claire Medical Corporation,** 900 Welch Road, Palo Alto, CA 94304, Tel (415) 321-9300.

COMPTON FOUNDATION HOSPITAL

820 West Compton Boulevard
COMPTON, CALIFORNIA 90220
(213) 537-3070
(213) 631-1148

G. CRESWELL BURNS, M.D.
Administrator and Medical Director

HELEN RISLOW BURNS, M.D.
Assistant Medical Director

MEMBER OF
American Hospital Association
and
National Association of Private Psychiatric Hospitals

High Standards of Psychiatric Treatment . . . Serving the Los Angeles Area

☆

Accredited by Joint Commission on Accreditation of Hospitals

What's on your patient's face...

may be more important than his chief complaint

Patient P.T.* seen on 3/29/67 shows typical lesions of moderately severe keratoses. Note residual scarring on ridge of nose from previous cryosurgical and electrosurgical procedures.

Patient P.T.* seen on 6/12/67, seven weeks after discontinuation of 5% FU cream. Reaction has subsided. Residual scarring not seen except that due to prior surgery. Inflammation has cleared and face is clear of keratotic lesions.

*Data on file, Hoffmann-La Roche Inc., Nutley, N.J

The lesions on his face are solar/actinic— so-called "senile" keratoses... and they may be premalignant.

Solar, actinic or senile keratoses

These lesions may be called by several names, but they usually can be identified by the following characteristics. The typical lesion is flat or slightly elevated, of a brownish or reddish color, papular, dry, rough, adherent and sharply defined. They commonly occur as multiple lesions, chiefly on the exposed portions of the skin.

Sequence of therapy— selectivity of response

After several days of therapy with Efudex® (fluorouracil), erythema may begin to appear in the area of the lesions; this reaction usually reaches its height of unsightliness and discomfort within two weeks, declining after discontinuation of therapy. This reaction occurs in affected areas. Since the response is so predictable, lesions that do not respond should be biopsied.

Acceptable results

Treatment with Efudex provides highly favorable cosmetic results. Incidence of scarring is low. This is particularly important with multiple facial lesions. Efudex should be applied with care near the eyes, nose and mouth.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Multiple actinic or solar keratoses.

Contraindications: Patients with known hypersensitivity to any of its components.

Warnings: If occlusive dressing used, may increase inflammatory reactions in adjacent normal skin. Avoid prolonged exposure to ultraviolet rays. Safe use in pregnancy not established.

Precautions: If applied with fingers, wash hands immediately. Apply with care near eyes, nose and mouth. Lesions failing to respond or recurring should be biopsied.

Adverse Reactions: Local—pain, pruritus, hyperpigmentation and burning at application site most frequent; also dermatitis, scarring, soreness and tenderness. Also reported—insomnia, stomatitis, suppuration, scaling, swelling, irritability, medicinal taste, photosensitivity, lacrimation, leukocytosis, thrombocytopenia, toxic granulation and eosinophilia.

Dosage and Administration: Apply sufficient quantity to cover lesion twice daily with nonmetal applicator or suitable glove. Usual duration of therapy is 2 to 4 weeks.

How Supplied: Solution, 10-ml drop dispensers—containing 2% or 5% fluorouracil on a weight/weight basis, compounded with propylene glycol, tris(hydroxymethyl)-aminomethane, hydroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate.

Cream, 25-Gm tubes—containing 5% fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

This patient's lesions were resolved with

Efudex®

fluorouracil/Roche®

5% cream/solution...a Roche exclusive

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine,** Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

ALCOHOLISM AND DRUG USE

April 20-21—**Alcoholism and Drug Abuse: 1974.** UCSF, CMA, Haight-Ashbury Free Medical Clinic, Institute for Social Concerns at UCSF. Saturday-Sunday. $60. Contact: UCSF.

CANCER

April 21—**Slide Seminar on Tumors of Female Genital Tract.** See Obstetrics and Gynecology, April 21.

April 27—**Cancer Viewpoints.** American Cancer Society, Contra Costa County Unit, at John Muir Hospital, Walnut Creek. Saturday. 4½ hrs. $7. Contact: Marian Lemke, Exec. Dir., 1341 E. Newell Ave., Walnut Creek 94596. (415) 934-7640.

May 30-31—**Cancer Symposium.** USC. Thursday-Friday.

July 22-25—**Cancer of the Skin and Mouth—Advances in Diagnosis and Treatment.** STAN. Monday-Thursday. 28 hrs. $200.

Continuously—**Tumor Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. Tuesdays, 4:00 p.m. Contact: Sidney Saltzstein, MD, University Hospital, San Diego. (714) 291-3330, ext. 1071.

Continuously — **Tumor Board — Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Pathology Conference Room, Harbor General Hospital, Torrance. Fridays 3-4 p.m. Advice and consultation from specialists in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: John Benfield, MD, Dept. of Surgery, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 281.

MEDICINE

April 18-19—**Coronary Rehabilitation.** USC. Thursday-Friday.

April 19—**Myocardial Infarction—New Therapeutic Approaches.** Santa Clara County Heart Association at Le Baron Hotel and Convention Center, San Jose. Friday. $20. Contact: Santa Clara Co. Heart Assn., Center for Cont. Ed. in Cardiovascular Disease, 1605 The Alameda, San Jose 95126.

April 22—**Clinical Spectrum of Coronary Artery Disease: Diagnosis and Treatment.** Mt. Zion Hospital and Medical Center at Holiday Inn, Redding. Monday. Contact: Mt. Zion Hosp. & Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600.

April 22-26—**Medical Diagnosis and Therapeutics in Internal Medicine.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. Monday-Friday.

April 24—**Clinical Spectrum of Coronary Artery Disease: Diagnosis and Treatment.** Mt. Zion Hospital and Medical Center at Doctors Hospital, Modesto. Wednesday. Contact: Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120. (415) 567-6600.

April 24-26—**Present Practice and New Developments in Nuclear Medicine.** See Radiology and Pathology, April 24-26.

April 26—**Clinical Spectrum of Coronary Artery Disease: Diagnosis and Treatment.** Mt. Zion Hospital and Medical Center at Del Monte Lodge, Carmel. Friday. Contact: Mt. Zion Hosp. & Med. Ctr., P.O. Box 7921, San Francisco 94102. (415) 567-6600.

May 3-5—**American Society of Internal Medicine.** Regency Hyatt House, San Francisco. Friday-Sunday. Contact: Mr. William R. Ramsey, 525 Hearst Bldg., 3rd and Market, San Francisco 94103.

May 4.—**Respiratory Care Workshop for Health Professionals.** Long Beach Lung Association at Edgewater Hyatt House, Long Beach. Saturday. 6 hrs. $10. Contact: Lorlon Roberts, Exec. Dir., Long Beach Lung Assn., 1002 Pacific Ave., Long Beach 90813. (213) 436-9873.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

May 9-10—**Advances in Cardiology.** USC at Huntington-Sheraton Hotel, Pasadena. Thursday-Friday.

May 15—**Sickle Cell Seminar on Current Research.** Charles R. Drew Postgraduate Medical School and King-Drew Sickle Cell Center at Claude Hudson Auditorium, Los Angeles. Wednesday. Contact: Duane Dillman, EdD, Coordinator of Cont. Ed., 1620 E. 119th St., Los Angeles 90059.

May 17—**California Heart Association—Scientific Sessions for Physicians.** Erawan Garden Hotel, Indian Wells. Friday. $25. Contact: Marilyn Probst, CHA, 1370 Mission St., San Francisco. (415) 626-0123.

May 19-20—**Peptic Ulcer Disease.** American Gastroenterological Association at Hilton Hotel, San Francisco. Sunday-Monday. $100 for members; $125 non-members. Contact: AGA Postgraduate Course-Peptic Ulcer, 6900 Grove Rd., Thorofare, N.J. 08086.

May 19-25—**American Gastroenterological Association.** Hilton Hotel, San Francisco. Sunday-Saturday. Contact: Mr. Charles B. Slack, Exec. Sec., AGA, 6900 Grove Rd., Thorofare, N.J. 08086.

May 20-21—**Gastrointestinal Endoscopy—4th Postgraduate Course.** American Society for Gastrointestinal Endoscopy at Hilton Hotel, San Francisco. Monday-Tuesday. $75 for ASGE members; $100 for non-members. Contact: J. Alfred Rider, MD, Dir., ASGE Postgraduate Course, 350 Parnassus, Suite 900, San Francisco 94117.

May 20-22—**Heart and Lung Disease in Neonates and Infants.** UCLA at Ahwahnee Hotel, Yosemite National Park. Sunday-Wednesday. For Southern Calif. physicians only.

May 22—**American Society for Gastrointestinal Endoscopy.** Hilton Hotel, San Francisco. Wednesday. Contact: Bernard M. Schuman, MD, Sec., ASGE, 2799 W. Grand Blvd., Detroit 48202.

May 23-25—**Cardiologists' Appraisal of Cardiac Surgery.** PMC at St. Francis Hotel, San Francisco. Thursday-Saturday.

Continuously—**Clinical Conferences.** Community Hospital of Santa Cruz. See Of Interest to All, Continuously.

Continuously—**Medical Chest Conference.** St. Mary's Hospital, San Francisco. Tuesdays, 4:00-5:00 p.m. in Pulmonary Classroom. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Medical Morbidity-Mortality Conference.** St. Mary's Hospital, San Francisco. Thursdays, 12:15-1:00 p.m. in Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Clinical Cardiology Conferences.** San Diego County Heart Association at University Hospital, San Diego. Thursdays, 8-10 p.m. Contact: Robert O'Rourke, MD, Instructor, Univ. Hospital, San Diego. (714) 291-3330, ext. 1644. Or Mrs. Cathy Ware, Prog. Dir., San Diego Co. Heart Assn., 3640 5th St., San Diego 92103. (714) 291-7454.

Continuously — **Differential Diagnosis in Internal Medicine.** USC. Fourth Thursday of each month, 7:30-10:00 p.m. September 27, 1973-May 30, 1974.

Continuously—**Renal Dialysis Traineeships.** UCSF. By special arrangement.

Continuously—**Preceptorships in Biochemistry and Biophysics.** UCSF. By arrangement.

Continuously—**Clinics in Dermatology.** UCSF. By arrangement.

Continuously—**Cardiovascular Seminars.** Mondays at 4:30 p.m. in the second floor lecture hall, Basic Science Building, UCSD. Contact: UCSD.

Continuously—**Preceptorships in Cardiology.** American College of Cardiology and PMC. By arrangement. Contact: Arthur Selzer,, MD, PMC; or Miss Mary Anne McInerny, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

Continuously—**Biomedical Lecture Series.** UCSD. Specified Wednesday at 8:00 p.m. For schedule contact UCSD.

Continuously—**Joint Continuing Medical Education Programs for South Bay Hospitals.** UCSD, Bay General Hospital, Chula Vista Community Hospital, Coronado Hospital, Paradise Valley Hospital and CRMP. Programs to be held at various hospitals. Contact: UCSD.

Continuously—**Neurology Conference.** San Joaquin General Hospital, Stockton. Mondays, 10:00-11:30 a.m. in Conference Room 2. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Renal Conference.** San Joaquin General Hospital, Stockton. First Thursday of each month, 11:00 a.m. to 12:00 noon, Conference Room 2. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Wednesday of each month, 10:00-11:30 a.m., Conference Room 1. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Seminar in Clinical and Public Health Aspects of Chest Diseases.** Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Three-hour sessions on second Friday of each month, 9-12 a.m., B-3 classroom, Chest Wards. Presentation of patients demonstrating medical, social, and public health aspects of chest disease, followed by discussion of cases. Course open to physicians, nurses, social workers and personnel concerned with detection and management of patients with chest disease. No fee. Contact: Matthew Locks, MD, Dir., Chest Ward Service, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1245.

Continuously—**Training of Physicians in Modern Concepts of Pulmonary Care.** CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George C. Burton, MD, LLU.

Continuously—**Neurological Sciences.** St. Francis Hospital of Lynwood. Wednesdays, 7:30-8:30 a.m. Presentations of radiological evaluations and pathological specimens of current material and review of current topics in specialty. Weekly notification of cases available. Contact: Ralph Miller, Admin. Asst., St. Francis Hospital of Lynwood, 3620 Imperial Hwy., Lynwood 90262. (213) 639-5111, ext. 365.

Continuously—**Continuing Education in Internal Medicine—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12:00-1:00 p.m. Systematic review of internal medicine, lectures by faculty and visiting professors. Contact: A. James Lewis, MD, Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 647.

Continuously—**Training for Physicians in General Internal Medicine.** CRMP Area VI and LLU at LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

Continuously—**Basic Home Course in Electrocardiography.** One year postgraduate series, ECG interpretation by mail. Physicians may register at any time. $125 (52 issues). Contact: USC.

Continuously—**Cardiology Conferences — CRMP Area III.** Monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations of local complicated cardiological problems. Contact: William J. Fowkes, Jr., MD, 703 Welch Road, Suite G1, Palo Alto 94304. (415) 321-1200, ext. 6015.

(Continued on Page 51)

When low back pain* interferes...

Help relieve pain, restore mobility with

PARAFON FORTE® Tablets

PARAFLEX® (chlorzoxazone)† 250 mg., TYLENOL® (acetaminophen) 300 mg

*This drug has been evaluated as "possibly" effective for this indication.

See brief summary of prescribing information on facing page for Indications, Contraindications, Warnings, Precautions and Adverse Reactions.

© McN 73

PARAFON FORTE® Tablets help relieve pain, restore mobility and stop pain-spasm feedback by providing:

a non salicylate analgesic equal to aspirin for relief of pain,[1,2] yet unlikely to cause the gastric irritation,[2,3] allergic reactions[2] or increased bleeding time[4] associated with aspirin therapy.

and a skeletal muscle relaxant shown in extensive clinical studies to be useful in a variety of low back disorders[5-7]* but which is not an antihistamine or tranquilizer derivative and is unlikely to produce a tranquilizing or sedative effect.[8]

***Indications** Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective for the relief of severe skeletal muscle pain and spasm when associated with acute disorders of the lower back (including acute exacerbations of chronic conditions).

Contraindications: Sensitivity to either component.
Warnings: *Usage in Pregnancy*—Use in woman of child-bearing potential only when potential benefits outweigh possible risks.
Precautions: Exercise caution in patients with known allergies or history of drug allergies. If a sensitivity reaction or any signs or symptoms suggestive of liver dysfunction are observed, the drug should be stopped.
Adverse Reactions: Occasionally, drowsiness, dizziness, lightheadedness, malaise, overstimulation or gastrointestinal disturbances may be noted; rarely, allergic-type skin rashes, petechiae, ecchymoses, angioneurotic edema or anaphylactic reactions. In rare instances, *Paraflex* (chlorzoxazone) may possibly have been associated with gastrointestinal bleeding. While *Paraflex* (chlorzoxazone) and chlorzoxazone-containing products have been suspected as being the cause of hepatic toxicity in approximately eighteen patients, it was not possible to state that the dysfunction was or was not drug induced.
Usual Adult Dosage: Two tablets q.i.d.
Supplied: Scored, light green tablets, imprinted "McNEIL"—bottles of 100.

References: **1.** Batterman, R.C., and Grossman, A.J.: Fed. Proc. *14*:316, 1955. **2.** Goodman, L.S., and Gilman, A., ed.: The Pharmacological Basis of Therapeutics, ed. 4. New York, The Macmillan Company, 1970. **3.** Vickers, F.N.: Gastroint. Endosc. *14*:94, 1967. **4.** Mielke, C.H., Jr., and Britten, A.F.H.: New Engl. J. Med. *282*:1270, 1970 (Corresp.). **5.** Vernon, W.G.: Curr. Therap. Res. *14*:801, 1972. **6.** Scheiner, J.J.: Curr. Therap. Res. *14*:168, 1972. **7.** Walker, J.M.: Curr. Therap. Res. *15*:248, 1973. **8.** Friend, D.G.: Clin. Pharmacol. Ther. *5*:871, 1964.

†U.S. Patent No. 2,895,877

McNEIL — McNeil Laboratories, Inc. Fort Washington, Pa. 19034

(Continued from Page 49)

Grand Rounds—Medicine

Tuesdays

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

9:00-10:00 a.m., Morrissey Hall, St. Mary's Hospital, San Francisco.

Neurologist in Chief Rounds. 12:30 p.m., 6 East, University Hospital of San Diego County, San Diego. UCSD.

Wednesdays

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

1st Wednesday of each month, 10:00-11:15 a.m., Conference Room 1, San Joaquin General Hospital, Stockton.

10:30-12 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:30 p.m., Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., University Hospital, UCSD.

12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

Thursdays

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

10:30-12:00 noon, Room 63-105, UCLA Medical Center. UCLA. Second, Third, and Fourth Thursdays.

Neurology. 11:00 a.m., 664 Science, UCSF.

Neurology. 12:30 p.m., University Hospital of San Diego County, San Diego. UCSD.

4th Thursday of each month, 12:30 p.m. in lower conference room, Huntington Intercommunity Hospital, Huntington Beach.

Fridays

8:00 a.m., Auditorium, First Floor, Kern County General Hospital, Bakersfield. UCLA.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. UCLA. Second and Fourth Fridays.

Neurology. 8:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

1st and 3rd Fridays, 8:30 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. UCLA.

Clinicopathologic Conference. 1st Friday, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

Internal Medicine. 2nd, 3rd, and 4th Fridays, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

MENTAL RETARDATION

May 23-24—**Aspects of Mental Retardation.** USC. Thursday-Friday.

June 3-15—**Mental Retardation.** UCLA. 13 days.

OBSTETRICS AND GYNECOLOGY

April 16-17—**Obstetrical Laparoscopy.** Charles R. Drew Postgraduate Medical School and Martin Luther King, Jr., General Hospital at Claude Hudson Auditorium, Los Angeles. Tuesday-Wednesday. Contact: Duane Dillman, EdD, Coordinator of Cont. Ed., 1620 E. 119th St. Los Angeles 90059.

April 20—**Short Stature Symposium.** See Pediatrics, April 20.

April 21—**Slide Seminar on Tumors of Female Genital Tract.** California Tumor Tissue Registry at Hilton Hotel, Pasadena. Sunday. Contact: Weldon K. Bullock, MD, Calif. Tumor Tissue Registry, 1200 N. State St., Box 40, Los Angeles 90033.

May 6-8—**Symposium on Gynecologic Endocrinology and Infertility.** USC at Royal Lahaina Hotel, Maui. Monday-Wednesday.

May 17-18—**Fetal Monitoring.** Memorial Hospital Medical Center-UCI Center for Health Education at Memorial Hospital Med. Ctr., Long Beach. Friday-Saturday. $50. Contact: D. V. Prian, MD, Memorial Hospital Med Ctr., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

Continuously—**Ob/Gyn Conference.** San Joaquin General Hospital, Stockton. Mondays, 12:00-1:30 p.m. in Doctors' Dining Room. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. See Radiology and Pathology, Continuously.

Grand Rounds—Obstetrics and Gynecology

Mondays

10-11:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Tuesdays

9:00 a.m., Fifth Floor Auditorium, Room 53-105, UCLA Medical Center. UCLA.

Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Center, Sacramento. UCD.

Fridays

8:00 a.m., Auditorium, Orange County Medical Center. UCI.

10:30 a.m., Auditorium, Women's Hospital, Los Angeles County-USC Medical Center, Los Angeles. USC.

Saturdays

8:00 a.m., Executive Dining Room, University Hospital of San Diego County, San Diego. UCSD.

PEDIATRICS

April 15-19—**Review of Pediatrics—4th Annual.** USC at Childrens Hospital, Los Angeles. Monday-Friday.

April 20—**Short Stature Symposium.** Division of Medical Genetics, Short Stature Clinic, Harbor General Hospital at Sacramento Inn, Sacramento. Saturday. Contact: Jim Kay, 5748 Straight Way, Carmichael 95608. (916) 445-2627.

May 9-11—**Advances in Pediatrics.** UCSF. Thursday-Saturday.

May 20-22—**Heart and Lung Disease in Neonates and Infants.** See Medicine, May 20-22.

June 13-14—**Infant Sensory Dysfunction.** USC. Thursday-Friday.

June 16-20—**1974 Birth Defects Conference.** Attending Staff Association, Harbor General Hospital at Newporter Inn, Newport Beach. Sunday-Thursday. Contact: David Rimoin, MD, Harbor Gen. Hosp., 1000 W. Carson, Torrance 90509. (213) 328-2380, ext. 1441.

June 21—**13th Annual Conference on Prematurity.** STAN. Friday.

Continuously—**Perinatal Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 12:30 p.m., Conference Room. Contact: Marguerite Markarian, MD, Dir. of Nurseries, Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3261.

Continuously—**Pediatric Clinical Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 8:00 a.m., Conference Room "H." Contact: Harry W. Orme, MD, Med. Dir., Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3228.

Continuously—**Preceptorships in Pediatrics.** UCSF. By arrangement.

Continuously—**Pediatric Cardiology Conference.** UCSD, Third Floor Conference Room, University Hospital. Clinical review of cases planned for the week, Tuesdays at 7:30 a.m.; Clinical review of data obtained, Fridays at 1:30 p.m. Contact: UCSD.

Continuously—**Pediatric Research Seminar.** UCSD. Mondays, 12 noon-1:00 p.m.

Continuously—**Pediatrics Clinical Conference.** San Joaquin General Hospital, Stockton. Wednesdays, 10:00-11:15 a.m., Conference Room 3. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric-Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Thursday of each month, 9:30-11:00 a.m., Conference Room 2. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric Cardiology Conference.** St. Vincent's Hospital, Los Angeles. Fourth Thursday of each month, 2:00 p.m., Main Doheny Conference Room. Contact: Leonard M. Linde, MD, Chief, Pediatric Cardiology, St. Vincent's Hospital, 3rd and Alvarado Sts., Los Angeles.

Continuously — **Pediatric Conference.** Cedars-Sinai Medical Center, Los Angeles. Thursdays weekly, 8:30-9:30 a.m. Contact: B. M. Kagan, MD, Lebanon Hall, Cedars-Sinai Med. Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 181.

Grand Rounds—Pediatrics

Tuesdays

8:00 a.m., Children's Hospital Medical Center, Oakland.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. UCLA.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

8:30 a.m., University Hospital of San Diego County, San Diego. UCSD.

11:30 a.m., Auditorium, Pediatric Pavilion, Los Angeles County-USC Medical Center, Los Angeles. USC.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Children's Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Children's Hospital, San Francisco.

Thursdays

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA.

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Pediatric Cardiology. 1st Friday of each month. 8:00 a.m., St. Vincent's Hospital, Los Angeles.

8-9:00 a.m., Lecture Hall, Children's Hospital of Los Angeles.

8:30 a.m., Room M104, Stanford University Medical Center, STAN.

8:30-9:30 a.m., alternately at St. Mary's, Children's, Mt. Zion, and Kaiser Hospitals, San Francisco.

9:30-11:00 a.m., Conference Room 2, San Joaquin General Hospital, Stockton.

Infectious Disease. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

PSYCHIATRY

May 18—**Teenage Sexual Problems and the Physician.** USC Continuing Education in Psychiatry at Hastings Auditorium, Hoffman Bldg., USC. Saturday. 6 hrs. $35. Contact: Donald H. Naftulin, MD, Dir., Cont. Ed. in Psych. USC Sch. of Med., 2025 Zonal Ave., L.A. 90033. (213) 225-1511, ext. 336.

June 1—**Stress.** UCSF. Saturday.

June 12—**The Impotent Male and the Liberated Female.** UCSF at Community Hospital, Santa Cruz. Wednesday.

June 24-28—**Comparative Psychotherapies.** USC Continuing Education in Psychiatry at Hilton Inn, San Diego. Monday-Friday. 20 hrs. $100. Contact: Donald H. Naftulin, MD, Dir., Cont. Ed. in Psych., USC. (213) 225-1511, ext. 336.

July 3-7—**Biofeedback for Physicians.** UCLA at Lake Arrowhead. Wednesday-Sunday.

Continuously—**Adolescent Case Review.** St. Mary's Hospital, San Francisco. Wednesdays, 1:00-2:00 p.m., 3 West Conference Room. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Preceptorships in Psychiatry.** UCSF. By arrangement.

Grand Rounds—Psychiatry

Wednesdays

10:30 a.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

11:00 a.m., McAuley Institute, St. Mary's Hospital, San Francisco.

RADIOLOGY AND PATHOLOGY

April 24-26—**Present Practice and New Developments in Nuclear Medicine.** American College of Physicians at Westbury Hotel, San Francisco. Wednesday-Friday. 18 hrs. $100 for ACP members; $150 for non-members. Contact: ACP, Registrar, Postgraduate Courses, 4200 Pine St., Philadelphia 19014.

April 26-27—**Laboratory Diagnosis of Immunologic Disorders.** UCSF. Friday-Saturday. 15 hrs. $100.

May 18—**Nuclear Medicine 1974—Tumor Localization, Bone and Bone Marrow Scanning.** UCD; Sierra Valley Nuclear Medicine Assn; No. Calif. Chapter, Society of Nuclear Medicine at Senator Hotel, Sacramento. Saturday. 4½ hrs.

May 31-June 2—**Radiology of the Pediatric Chest.** American College of Radiology at San Diego. Friday-Sunday. 15 hrs. $200 for members; $240 for non-members. Contact: ACR, 6900 Wisconsin Ave., Chevy Chase, Md. 20015.

June 11-14—**Society of Nuclear Medicine.** Town and Country Hotel, San Diego. Tuesday-Friday. Contact: Margaret Glos, Exec. Dir., SNM, 305 E. 45th St., N.Y. 10017.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. Mondays, 12:00 noon, Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Pathology Conference.** St. Mary's Hospital, San Francisco. 2nd and 4th Wednesdays. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Tumor Board.** St. Mary's Hospital, San Francisco. Mondays, 8:00-9:00 a.m., Clinic Building, Room 3. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Clinical Pathology Conference.** St. Mary's Hospital, San Francisco. Third Tuesday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Radiology Film Reading Sessions.** Orange County Radiology Society and Orange County Medical Center at Orange County Medical Center, Orange. 1st Tuesday of each month, September-June, 7:30-9:00 p.m. Contact: Edward J. Miller, MD, 301 Newport Blvd., Newport Beach. (714) 645-8600.

Continuously—**Cytopathology Seminars.** UCSF. 2nd Thursday of each month, September-June. 5:00-6:00 p.m. Contact: Eileen King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously — **Cytopathology Tutorial Program.** UCSF. Courses may be arranged throughout the year on the basis of individual needs and goals; fees are prorated accordingly. Arrangements should be discussed with instructor, Eileen B. King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two-part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

Continuously—**Scintillation Camera Workshop.** UCSF. Workshops provided for physicians and nuclear medicine technologists by special arrangement, limited to 30 trainees per workshop. One- or two-day intensive training periods, basic instruction in scintillation camera theory, scintographic principles and scintiphotographic interpretations. $50. Contact: UCSF.

Continuously — **Scintiphotograph Interpretation.** UCSF and Nuclear Medicine Section, Department of Radiology, UCSF. By special arrangement, designed to furnish physicians with an opportunity to participate in the daily activities of a university laboratory. Two-week training period participation in daily interpretation conferences, correlation conferences, routine training conferences. $175. Contact: UCSF.

Grand Rounds—Radiology-Pathology

Mondays

Pathology. 1:00 p.m., Sacramento Medical Center, Sacramento. UCD.

Tuesdays

Radiology. 3rd Tuesday of each month, 8:00 a.m., Bothin Auditorium, Children's Hospital and Adult Medical Center, San Francisco.

SURGERY AND ANESTHESIOLOGY

April 17-21—**Vascular Surgery—2nd Annual.** UCLA at Riviera Hotel, Palm Springs. Wednesday-Sunday.

April 18—**Anesthesia.** California Society of Anesthesiologists, Inc., at Regency Hyatt Hotel, San Francisco. Thursday. Contact: CSA, 100 S. Ellsworth Ave., Suite 411, San Mateo 94401. (415) 343-4644.

April 20—**Surgical Anatomy and Surgery of the Abdomen.** International College of Surgeons, Southern Calif. Division, at Los Angeles Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Darline Murphy, Ex. Sec., ICS, So. Calif. Div., 136 N. Brighton, Burbank 91506. (213) 846-0669.

April 22-27—**American Academy of Neurology.** St. Francis Hotel, San Francisco. Monday-Saturday. Contact: Mr. Stanley A. Nelson, Exec. Dir., 4005 W. 65th St., Minneapolis, Minn. 55435.

April 26—**Anesthesia and Acupuncture as Currently Practiced in the People's Republic of China.** California Society of Anesthesiologists, Inc., at Newporter Inn, Newport Beach. Friday. Contact: CSA, 100 S. Ellsworth Ave., Suite 411, San Mateo 94401. (415) 343-4644.

April 27—**Anesthesia and Acupuncture as Currently Practiced in the People's Republic of China.** California Society of Anesthesiologists, Inc., at Hilton Hotel, Los Angeles. Saturday. Contact: CSA, 100 S. Ellsworth Ave., Suite 411, San Mateo 94401. (415) 343-4644.

April 28-May 5—**Management of the Surgical Patient.** STAN at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week.

April 29-May 2—**Southwestern Surgical Congress.** Del Monte Hyatt House, Monterey. Monday-Thursday. Contact: Jack A. Barney, MD, Sec.-Treas., 708 Physicians and Surgeons Bldg., Oklahoma City, Okla. 73103.

May 2-3—**Ocular Pharmacology and Therapeutics.** UCLA, Jules Stein Eye Institute, at Neuropsychiatric Institute Auditorium, UCLA. Thursday-Friday. Contact: Bradley R. Straatsma, MD, or Leonard Apt, MD, Course Chairmen, Jules Stein Eye Institute, UCLA Sch. of Med., Los Angeles 90024. (213) 825-5053.

May 3-4—**Trauma.** UCSF at Mary's Help Hospital, Daly City. Friday-Saturday.

May 5-8—**Rhinoplasty.** UCLA. Sunday-Wednesday.

May 9-10—**Phaco-Fragmentation.** UCSF. Thursday-Friday.

May 9-11—**Neurosurgery.** UCSF at Hilton Hotel, San Francisco. Thursday-Saturday. 21 hrs. $100.

May 9-11—**Disability of the Hand: Prevention, Assessment and Treatment.** American Society for Surgery of the Hand at Hyatt on Union Square, San Francisco. Thursday-Saturday. 18 hrs. $150. Contact: Eugene Kilgore, MD, 450 Sutter St., San Francisco. (415) 956-2525.

May 10-12—**Low Back Pain.** UCLA. Friday-Sunday.

May 17—**Neurology.** USC. Friday.

May 18—**Surgical and Clinical Anatomy of the Vascular System.** International College of Surgeons, So. Calif. Division, at Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Darline Murphy, Ex. Sec., 136 N. Brighton, Burbank 91506. (213) 846-0669.

May 21-22—**Society for Surgery of the Alimentary Tract.** Hilton Hotel, San Francisco. Tuesday-Wednesday. Contact: Robert Zeppa, MD, Sec., P.O. Box 875, Biscayne Annex, Miami 33152.

May 23-25—**Cardiologists' Appraisal of Cardiac Surgery.** See Medicine, May 23-25.

May 30-June 2—**California Society of Anesthesiologists Inc.—Annual Scientific Meeting.** Sahara Tahoe Hotel, Lake Tahoe. Wednesday-Saturday. 15 hrs. Contact: Norman R. Catron, Ex. Sec., 100 S. Ellsworth Ave., Suite 400, San Mateo 94401. (415) 343-4644.

June 9-13—**Pacific Coast Oto-Ophthalmological Society.** Hotel del Coronado, Coronado. Sunday-Thursday. $35 for members; $50, non-members. Contact: Daniel G. Vaughan, MD, Exec. Sec., Room 494U, UCSF, San Francisco 94143. (415) 666-1993.

June 12-16—**Barany Society.** Disneyland Hotel, Anaheim. Wednesday-Sunday. $200. The program of this international vestibular society will be devoted to the problem of Meniere's disease. Contact: Jack L. Pulec, MD, Otologic Medical Group, Inc., 2122 W. 3rd St., Los Angeles 90057.

June 15—**Orthopaedic Surgery and Surgical Anatomy of the Neck and Upper Extremity.** International College of Surgeons, So. Calif. Division, at L.A. Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Darline Murphy, Exec. Sec., 136 N. Brighton, Burbank 91506. (213) 486-0669.

June 15-16—**Techniques in Respiratory Therapy.** American Society of Anesthesiologists at St. Francis Hotel, San Francisco. Saturday-Sunday. 13 hrs. $75 for members; $100, nonmembers. Contact: ASA, 515 Busse Highway, Park Ridge, Ill. 60068. (312) 825-5586.

June 22—**Ophthalmology Clinical Conference.** STAN. Saturday.

June 27-28—**Highlights of Modern Ophthalmology.** PMC. Thursday-Friday. 16 hrs.

July 1-Sept. 13—**Basic Science Course in Ophthalmology,** STAN. 6 wks.

Continuously—**Basic Science Lecture Series.** Dept. of Surgery, St. Mary's Hospital, San Francisco. Mondays, 11:15 a.m.-12:15 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Mini Residencies in Orthopaedics.** STAN. Postgraduate traineeships of 4-14 days duration, as you wish. No tuition but donations accepted. Contact: Orthopaedic Division, Dept. of Surgery, Stanford.

Continuously—**Orthopedic Lecture Series.** Alternately at St. Mary's, St. Joseph's, Mary's Help, VA Martinez, Kaiser San Francisco, and Harkness Memorial Hospitals. Third Tuesday of each month, 6:00 p.m. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Orthopedic Trauma Conference.** USC at Los Angeles County-USC Medical Center. Mondays, 7:00-9:00 p.m. Contact: Dept. of Orthopedics, USC School of Med., 2025 Zonal Ave., Los Angeles 90033. (213) 225-3131.

Continuously—**Preceptorships in General Surgery.** UCSF. By arrangement.

Continuously—**Preceptorships in Neurological Surgery.** UCSF. By arrangement.

Continuously—**Preceptorships in Urology.** UCSF. By arrangement.

Continuously—**Training for Physicians in Nephrology.** CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Stewart W. Shankel, MD, LLU.

Continuously—**Surgical Anatomy.** St. Mary's Hospital, San Francisco. Mondays, 4:30 p.m., St. Mary's Hall, 2 W. Classroom. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Cline Clinic.** St. Mary's Hospital, San Francisco. Mondays, 1:30 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Morbidity and Mortality Conference.** 4th Monday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Surgical Pathology Conference.** See Radiology/Pathology, Continuously.

Continuously—**Thoracic Surgery Conference.** San Joaquin General Hospital, Stockton. Fourth Wednesday of each month, 9:00-10:30 a.m., Conference Room 1. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Medical Surgical Combined Conference.** San Joaquin General Hospital, Stockton. Second Wednesday of each month, 10:00-11:15 a.m., Conference Room 1. Contact: J. David Bernard, MD, FACP, Dir. of Med. Ed., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Orthopaedic Audio-Synopsis Foundation.** A nonprofit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Twelve monthly c-60 cassette tapes. Annual subscription rate $72 ($36 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

Grand Rounds—Surgery

Mondays

9-10 a.m., Morrissey Hall, St. Mary's Hosiptal, San Francisco.

Tuesdays

Orthopedic Surgery. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:00-10:00 a.m., San Joaquin General Hospital, Stockton.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. UCLA.

3:30 p.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

Neurology and **Neurosurgery.** 11:00-12:15, Room 663, Science Building, UCSF.

Fridays

1:00-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego, UCSD.

Urology. 8:00 a.m., 3rd floor conference room, University Hospital of San Diego County, San Diego. UCSD.

Orthopedics. 8:00-9:00 a.m. St. Mary's Hospital, San Francisco.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA.

Orthopedics. 10:00 a.m. Auditorium of the Children's Division, Los Angeles County-USC Medical Center. The third Saturday of each month. USC.

OF INTEREST TO ALL PHYSICIANS

April 16-18—**Family Practitioners: Heart Oriented Clinical Office Practice.** UCLA. Tuesday-Thursday.

April 18-20—**Eighth National Congress on the Socio-Economics of Health Care.** American Medical Association at Town and Country Hotel, San Diego, Thursday-Saturday. Contact: AMA, 535 N. Dearborn St., Chicago 60610.

April 19-20—**Conference on Physical Fitness and Sports Medicine.** California Medical Association at Hilton Inn, San Diego. Friday-Saturday. Contact: Richard Manley, CMA.

April 20—**Short Stature Symposium.** See Pediatrics, April 20.

April 20—**The Role of Nutrition in Medicine.** UCD. Saturday.

April 22-28—**An Introduction to Diving Medicine.** UCSF at VA Hospital, Fresno. Wednesday-Sunday.

April 26—**Educational Methodology I—Simulation and Video.** PMC. Friday. For directors of medical education.

April 26-28—**International College of Applied Nutrition.** Biltmore Hotel, Los Angeles. Friday-Sunday. Contact: Mrs. Harold Stone, Exec. Sec., P.O. Box 386, La Habra 90631.

May 3-4—**San Joaquin Valley Counties Regional Postgraduate Institute.** CMA at Ahwahnee Hotel, Yosemite National Park. Friday-Saturday. Contact: Richard Manley, CMA.

May 8—**Clinic on Obesity.** UCSF at Community Hospital, Santa Cruz. Wednesday.

May 9-11—**Disability of the Hand: Prevention, Assessment and Treatment.** See Surgery, May 9-11.

May 11—**Current Concepts in Drug Therapy for the Practicing Physician—5th Annual Symposium in Clinical Pharmacology.** STAN, Palo Alto Medical Clinic, Palo Alto Medical Research Foundation at Stanford. Saturday.

May 15—**Office Orthopedics.** Alameda-Contra Costa Chapter, Calif. Academy of Family Physicians, at Edgewater Hyatt House Hotel, Oakland. Wednesday. Contact: Gordon Benner, MD, 3000 Colby St., Berkeley. (415) 848-7533.

May 15—**Changing Patterns in the Practice of Medicine—Annual Medical Staff Symposium.** Memorial Hospital Medical Center of Long Beach. Wednesday. Contact: H. David Mosier, MD, Prog. Comm. Chrm., Memorial Hosp. Med. Ctr., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3236.

May 18—**Utilization Review in Hospitalized Patients.** UCSF at St. Francis Hospital, San Francisco. Saturday.

May 30-June 1—**American College of Emergency Physicians, California Chapter—3rd Annual Scientific Assembly.** Fairmont Hotel, San Francisco. Thursday-Saturday. 16 hrs. Contact: Karl G. Mangold, MD, 897 MacArthur Blvd., Suite 101, San Leandro 94577. (415) 638-3979.

June 6—**Drug Therapy and Pharmacy.** USC. Thursday.

June 12—**The Impotent Male and the Liberated Female.** See Psychiatry, June 12.

June 15-16—**Current Fads in Dietetics.** UCLA. Saturday-Sunday.

June 16-20—**1974 Birth Defects Conference.** See Pediatrics, June 16-20.

Continuously—**Clinical Problems in Daily Practice: Physiological Basis and Practical Management.** UCSF at Chinese Hospital, San Francisco. 1st Tuesday of each month; 8:00-9:30 p.m. Apr.—Practical Approach to Diagnosis & Management of Stroke; May—A Critical Overview of Antibiotic Therapy; June—The Patient in Respiratory Failure; July—Diabetes Mellitus; Aug.—Congestive Heart Failure; Sept.—Jaundice; Oct. & Nov.—to be announced.

Continuously—**Clinical Conferences.** UCSF and Community Hospital of Santa Cruz at Community Hospital, Santa Cruz. 2nd Wednesday of each month, Oct. 10, 1973-June 12, 1974, 11:00 a.m.-2:30 p.m. 27 hours. $50 for series; $7.50 per lecture. Apr.—Management of Acute Trauma; May—Clinic on Obesity; June—The Impotent Male and the Liberated Female.

Continuously—**Emergency Medicine.** USC. Wednesdays, 7:30-9:30 p.m.

Continuously—**Bedside Clinics.** See Medicine, Continuously.

Continuously—**Family Health Program—Southern California.** 2925 N. Palo Verde, Long Beach. Second Friday of each month. 1:00-2:00 p.m. Contact: UCI.

Continuously — **Lecture Program.** Riverside-San Bernardino Chapter, American Academy of Family Physicians and UCI at Ram's Horn Inn, San Bernardino. 3rd Thursday of each month. 7:30 p.m. Contact: UCI.

Continuously—**Lecture Program.** UCI and Orange County Chapter, American Academy of Family Physicians at Saddleback Inn, Santa Ana. 2nd Monday of each month, 7:30 p.m. Contact: UCI.

Continuously—**Hospital Lecture Program.** UCI at Anaheim Mem. Hosp.; Brea Comm. Hosp.; Fountain Valley Comm. Hosp.; Garden Park Gen. Hosp., Anaheim; Hartland Comm. Hosp., Baldwin Park; Huntington Intercomm. Hosp., Huntington Beach; Imperial Gen. Hosp., Inglewood; La Habra Comm. Hosp.; La Mirada Comm. Hosp.; Los Alamitos Gen. Hosp.; Mission Comm. Hosp., Mission Viejo; Palm Harbor Hosp., Garden Grove; Rio Hondo Mem. Hosp., Downey; San Gabriel Valley Comm. Hosp., San Gabriel; Stanton Comm. Hosp.; Studebaker Comm. Hosp., Norwalk; West Anaheim Gen. Hosp.; Westminster Comm. Hosp. Contact: UCI.

Continuously—**Professional Education Program.** Porterville State Hospital. Contact: Frank McCarry, MD, P.O. Box 2000, Porterville. (209) 784-2000.

Continuously—**Round Tables with Pacific Medical Center.** PMC and Sonoma Valley Hospital at Sonoma Valley Hospital, Sonoma. Second Monday of each month in Dining Room of the hospital, 8:00-10:00 p.m. $100 per series, $15 per session. Contact: William J. Newman, MD, P.O. Box B, Sonoma 95476. (707) 996-3621.

Continuously—**Basic Science Lecture Series.** UCSD Mondays, 4:00 p.m., third floor conference room, University Hospital of San Diego County, San Diego. Contact: UCSD.

Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: General Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $75 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

Continuously—**Medical Media Network.** Programs and study guides produced in association with faculties of major medical schools and centers throughout California. MMN administered by University Extension, UCLA. Subscriptions for all California hospitals, rental or purchase, 16 mm, super 8 mm, one-inch videotape. Provides physicians throughout the state with current educational programs in local hospitals. Consult the nearest MMN Hospital regarding time and date for viewing. Contact: Mr. David E. Caldwell, Exec. Dir., MMN, 10995 Le Conte Ave., Los Angeles 90024. (213) 825-1791.

Continuously—**Stanford Speaker's Bureau for Environmental Topics.** Stanford University Committee for Environmental Information. Provides on request speakers and programs on environmental topics. Air pollution, water pollution and water conservation issues, radiation hazards and radiation technology, pesticides and their ecological problems, medicine's responsibilities in the environmental-ecology crisis and others. Contact: STAN.

Continuously—**Stanford-Mills Memorial Hospital Continuing Education Program.** STAN at Mills Memorial Hospital, San Mateo. Tuesday-Friday weekly. Basic Science for the Clinician, Grand Rounds, Intensive Care. Contact: STAN.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

FAMILY PRACTICE

April 17-19—**Sommer Memorial Lectures.** Benson Hotel, Portland.

MEDICINE

April 24—**Traumatic Emergencies.** Corvallis. Contact: Circuit Course Program, Oregon Medical Association. 4 Credits OAFP and OMA. Tuition $20.

May 15-17—**Combined American College of Emergency Physicians, Emergency Department Nurses Association, and Emergency Medical Technicians.** Contact: Donald L. McNeill, MD, Good Samaritan Hospital, 1015 N.W. 22nd, Portland 97210.

May 23—**Symposium on Prostaglandin.** University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201. Contact: M. Roberts Grover, Jr., MD, Associate Dean, University of Oregon Medical School, (503) 225-8228.

SURGERY

April 24-25—**The Pre-Surgical Back Problem.** Ramada Inn, Tualatin 97062. 10¾ prescribed credits OAFP and OMA. Contact: Rolland A. Martin, MD, Workmens Compensation Board of the State of Oregon, 219 Labor & Industries Building, Salem 97310.

MEDICAL GRAND ROUNDS

April 24—8:00 a.m.—Providence Hospital, Portland—Multi-Element Echocardiography.

May 21—7:00 p.m.—Providence Hospital, Portland—Consequences and Cures of the Use of Prescription Drugs.

OF INTEREST TO ALL PHYSICIANS

April 24-25—Salem and Newport. **Hypertension.** Contact: Circuit Course Program, Oregon Medical Association, 2164 S.W. Park Place, Portland 97205. (503) 226-1555. 4 credits OAFP and OMA. Tuition $20.00.

WASHINGTON, MONTANA and ALASKA

REGIONAL MEDICAL PROGRAM

THIS LISTING of continuing medical education activities in Washington, Montana, and Alaska is supplied by Washington/Alaska Regional Medical Program. In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

April 18-19. **Neurology and Psychiatry.** Thursday-Friday. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. School of Med. E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

April 19—**Tacoma Surgical Club—Annual Meeting.** Univ. of Puget Sound, Tacoma. Friday. Contact: Thomas J. Miskovsky, MD, 919 South 9th, Tacoma 98405. (206) MA 7-7143.

April 25-26—**Repiratory Care.** Health Sciences Thursday-Friday. 13 hrs. $75. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

April 26-27—**Clinical Cancer Conference.** Friday-Saturday. $50. Edgewater Inn. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

April 29-30. **Exercise Testing Workshop.** Monday-Tuesday. $80. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

May 2-3—**Death and Dying.** Health Sci. Audit., Thursday-Friday. 13 hr. Fee not set. Contact: Richard L. Reimer, Asst. Dir., CME, Univ. of Wash Sch. of Med., E-305 HSB, SC-50, Seattle 98195. (206) 543-1050.

May 6-10—**Emergency Medicine for Career Emergency Physicians.** UW. Monday-Friday. 43 hrs. $200. Contact: Richard L. Reimer, Asst. Dir., E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 11-12—**Diagnostic and Therapeutic Radiology.** Pacific Northwest Radiological Society Annual Meeting. Washington Plaza Hotel, Seattle. Saturday-Sunday. Contact: Arthur R. Griffin, MD, 455 Medical-Dental Bldg., Seattle 98101. (206) 682-2218.

May 12-16—**American Association of Plastic Surgeons.** Olympic Hotel, Seattle. Sunday-Thursday. Contact: Maurice J. Jurkiewicz, Emory University Affiliated Hospital, 69 Butler St., S.W., Atlanta, Georgia 30303.

May 15-17—**Advances in Internal Medicine.** Wednesday-Friday. Health Sciences. 18 hrs. $75. Contact: Richard L. Reimer, Asst. Dir., E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 16-17—**Kids and More in '74.** Thursday-Friday. 13 hrs. Fee not set. Contact: William O. Robertson, Children's Orthopedic Hospital, 4800 Sandpoint Way, Seattle 98105. (206) 634-5072.

May 17-18—**Problems in Gastrointestinal Surgery.** Friday-Saturday. Virginia Mason Medical Center Auditorium. 9 hrs. $35. Contact: Kenneth Wilske, MD, Dir., CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA3-3700 ext. 470.

May 24-25—**Hypertension: Etiology and Factors in Choice of Drugs.** Friday-Saturday. Virginia Mason Clinic Medical Center Auditorium. 13 hrs. $50. Contact: Kenneth Wilske, MD., Dir. CME, Virginia Mason Clinic Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA3-3700 ext. 470.

May 30-June 1—**Washington Academy of Family Physicians Annual Meeting.** Holiday Inn, Spokane. Thursday-Saturday. Contact: John P. Plastino, MD, 6th Ave. Medical Bldg., Spokane 99204.

June 7-8—**Interpretation of Liver Biopsies.** Friday-Saturday. Virginia Mason Medical Center Auditorium. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA3-3700 ext. 470.

June 28-29—**Diagnosis and Management of Diffuse Pulmonary Infiltrates.** Friday-Saturday. Virginia Mason Medical Center Auditorium. 9 hrs. $35. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA3-3700 ext. 470.

Index to The Western Journal of Medicine Advertising

American Medical Writers Association 44

Ayerst Laboratories
Premarin 12, 13

Bank of America 3

Bio-Science Laboratories
Laboratory Service 25

Breon Laboratories, Inc.
Bronkotabs 10

Burroughs Wellcome Co.
Neosporin 33

Classified 30, 45

Compton Foundation 45

Dorsey Laboratories
Triaminic Expectorant 19
Triaminic Syrup 29

Eli Lilly and Company
Darvocet-N 32

Mead Johnson Laboratories
Vasodilan 24

Medical Economics
Cassette Service 39

Marion Laboratories Inc.
Nico-400 ..... 34, 35

McNeil Laboratories
Parafon Forte 50, 51

Merck Sharp & Dohme
Triavil 20, 21, 22
Aldomet 36, 37, 38

Pharmaceutical Manufacturers Association
Prescription Ads 8, 9

Presto Food Products, Inc.
Matey 31

The Purdue Frederick Company
Senecot (Geriatric) 5
Senecot (Cardiac) 42
Senecot (Drug-Induced) ..... Back Cover

Ritter Company
Kryostik 43

A. H. Robins Co.
Dimetapp/Phenaphen 17, 18

Roche Laboratories
Dalmane ..... 2nd Cover and Page 1
Librium 6, 7
Bactrim 14, 15, 16
Efudex 46, 47

Safeguard Business Systems Inc. 40

G. D. Searle & Co.
Pro-Banthine ..... 58 and 3rd Cover

Security Pacific National Bank 28

Smith Kline & French Laboratories
Dyazide 11

State Compensation Insurance Fund 23

Warner-Chilcott Laboratories
Proloid 40, 41

Wine Institute 4

Wyeth Laboratories
Wycillin/Bicillin 26, 27

how to civilize the of peptic ulcer...

give pain killers?...prescribe frequent eating?...use antacids only?

give pain killers only?

They relieve pain but may cause patient drug dependency and unnecessary sedation.

prescribe frequent eating only?

Frequent feeding helps buffer acid, but caloric, digestive, and social considerations make frequent eating both difficult and impractical.

use antacids only?

Antacids, like food, help neutralize or buffer stomach acidity. Their action is short, usually lasting only 1 to 1½ hours (given four hours after a meal).* Some patients may require antacids every half hour.

When you add Pro-Banthine® you

brand of
propantheline bromide

Indications: Pro-Banthine is effective as adjunctive therapy in the treatment of peptic ulcer. Dosage must be adjusted to the individual.

Contraindications: Glaucoma, obstructive disease of the gastrointestinal tract, obstructive uropathy, intestinal atony, toxic megacolon, hiatal hernia associated with reflux esophagitis, or unstable cardiovascular adjustment in acute hemorrhage.

Warnings: Patients with severe cardiac disease should be given this medication with caution.

Fever and possibly heat stroke may occur due to anhidrosis.

In theory a curare-like action may occur, with loss of voluntary muscle control. For such patients prompt and continuing artificial respiratio should be applied until the drug effect has been exhausted.

Diarrhea in an ileostomy patient may indicate obstruction, and th possibility should be considered before administering Pro-Banthine.

Precautions: Since varying degrees of urinary hesitancy may be evidence by elderly males with prostatic hypertrophy, such patients should b advised to micturate at the time of taking the medication.

Overdosage should be avoided in patients severely ill with ulcerati colitis.

Adverse Reactions: Varying degrees of drying of salivary secretions m

cannibal stomach

add Pro-Banthīne

Helps to relieve pain without risk of patient drug dependency.

add Pro-Banthīne

Reduces gastric secretory volume and total resting and free acid without the caloric, digestive, and social problems occasioned by frequent eating.

add Pro-Banthīne

Pro-Banthīne slows intestinal motility to enhance and prolong the action of antacids. The action of Pro-Banthīne lasts 4 to 6 hours.

*Fordtran, J. S., and Collyns, J. A. H.: Antacid Pharmacology in Duodenal Ulcer: Effect of Antacids on Postcibal Gastric Acidity and Peptic Activity, New England J. Med. 274:921-927 (April 28) 1966.

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Address medical inquiries to: G. D. Searle & Co. Medical Department, Box 5110, Chicago, Ill. 60680

usually get better patient response.

cur as well as mydriasis and blurred vision. In addition the following verse reactions have been reported: nervousness, drowsiness, dizziness, omnia, headache, loss of the sense of taste, nausea, vomiting, constipa-n, impotence and allergic dermatitis.

osage and Administration: The recommended daily dosage for adult al therapy is one 15-mg. tablet with meals and two at bedtime. Subse-ent adjustment to the patient's requirements and tolerance must be ade.

o-Banthīne P.A.—Each tablet of Pro-Banthīne P.A. (propantheline omide) contains 30 mg. of the drug in the form of sustained-release or timed-release beads; on ingestion about half of the drug is released within an hour and the remainder continuously as earlier increments are metab-olized. Thus the result is even, high-level anticholinergic activity main-tained all day and all night in most patients with only two tablets daily. Some patients may require one tablet every eight hours.

The contraindications and precautions applicable to Pro-Banthīne 15 mg. should be observed.

How Supplied: Pro-Banthīne is supplied as tablets of 15 and 7.5 mg., as prolonged-acting tablets of 30 mg. and, for parenteral use, as serum-type vials of 30 mg.

situation:

Chronic disease...requires constant medication...often several different drugs...

constipation:

A number of drugs may interfere with the regular bowel action...antacids, anticholinergics, narcotics, antispasmodics, barbiturates, antihypertensives, antidepressants, tranquilizers... and many others...

laxation:

SENOKOT Tablets or Granules effectively counteract drug-induced constipation... do not interfere with primary medication ...act gently and predictably.

Supplied: SENOKOT Tablets (small, easy-to-swallow)—Bottles of 50 and 100. SENOKOT Granules (delicious, cocoa-flavored)—4 ,8 and 16 ounce (1 lb.) canisters.

SENOKOT Tablets Granules

(standardized senna concentrate)

a natural laxative

PURDUE FREDERICK

© COPYRIGHT 1974, THE PURDUE FREDERICK COMPANY
NORWALK, CONN. 06856 A7286 136974

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON
MAY 21 1974

THE WESTERN Journal of Medicine

VOLUME 120 • NUMBER 5 **MAY 1974**

353 *Conservative and Surgical Aspects of Disc Lesion Management—Follow-Up Review of 244 Cases* LESLIE BLAU, MD, and LEON KENT, MD

358 *Diabetes Mellitus—Distinguishing Between Patients Receiving Insulin and Those Requiring Insulin Therapy* RICHARD J. MAHLER, MD

363 *Differential Antibiotic Excretion in Unilateral Structural Pyelonephritis* JOHN M. PALMER, MD

SPECIALTY CONFERENCE

369 *Viral Infections of the Fetus*
Moderator: DAVID T. IMAGAWA, PhD; Discussants: MILAN FIALA, MD, JOSEPH W. ST. GEME, JR, MD, and TERRY YAMAUCHI, MD
Teaching Conference in Infectious Diseases, UCLA School of Medicine, Harbor General Hospital, Torrance, California

PSYCHIATRIC ROUNDS

376 *Male Transsexualism*
Chairman: ARNOLD MANDELL, MD; Case Presentation: STEPHEN MILLMAN, MD; Discussants: ROBERT GERNER, MD, LEWIS JUDD, MD, ZANE PARZEN, MD, and ROBERT STOLLER, MD

Editorial Comment—Gender Dysphoria Syndrome NORMAN M. FISK, MD

MEDICAL STAFF CONFERENCE

392 *The Problem of Diagnosis and Classification of Chronic Hepatitis*
Discussion by MARTIN BROTMAN, MD

400 IMPORTANT ADVANCES IN CLINICAL MEDICINE—*Pediatrics*

407 EDITORIALS • *Viral Infection of the Fetus* • *National Health Insurance—Are We Really Ready for It Yet?*

CASE REPORTS

410 *Functional Recovery in Older Patients After Prolonged Oliguria*
MARY LU SANFELIPPO, MD, LARRY E. BENSON, MD, and DAVID L. McCULLOUGH, MD

412 *Tricuspid Valve Replacement in Carcinoid Heart Disease*
HAROLD G. LUND, MD, RICHARD J. CLEVELAND, MD, LOWELL H. GREENBERG, MD, MAURICE LIPPMANN, MD, and MALIN R. DOLLINGER, MD

416 *Hypothalamic-Hypothyroidism Secondary to Sheehan's Syndrome*
PETER A. SINGER, MD, JORGE H. MESTMAN, MD, PHIL R. MANNING, MD, and JOHN T. NICOLOFF, MD

419 LETTERS TO THE EDITOR

TRAUMA ROUNDS

421 *Management of Pelvic Fractures*
Chief Discussant: MICHAEL CHAPMAN, MD; Editors: DONALD D. TRUNKEY, MD, and F. WILLIAM BLAISDELL, MD

GOVERNMENT AND MEDICINE

425 *The Curious Odyssey of Regional Medical Programs* PAUL D. WARD

SPECIAL ARTICLE

430 *Medicine and Public Health in the People's Republic of China—Observations and Reflections of a Recent Visitor* PHILIP R. LEE, MD

MEDICINE IN SOCIETY

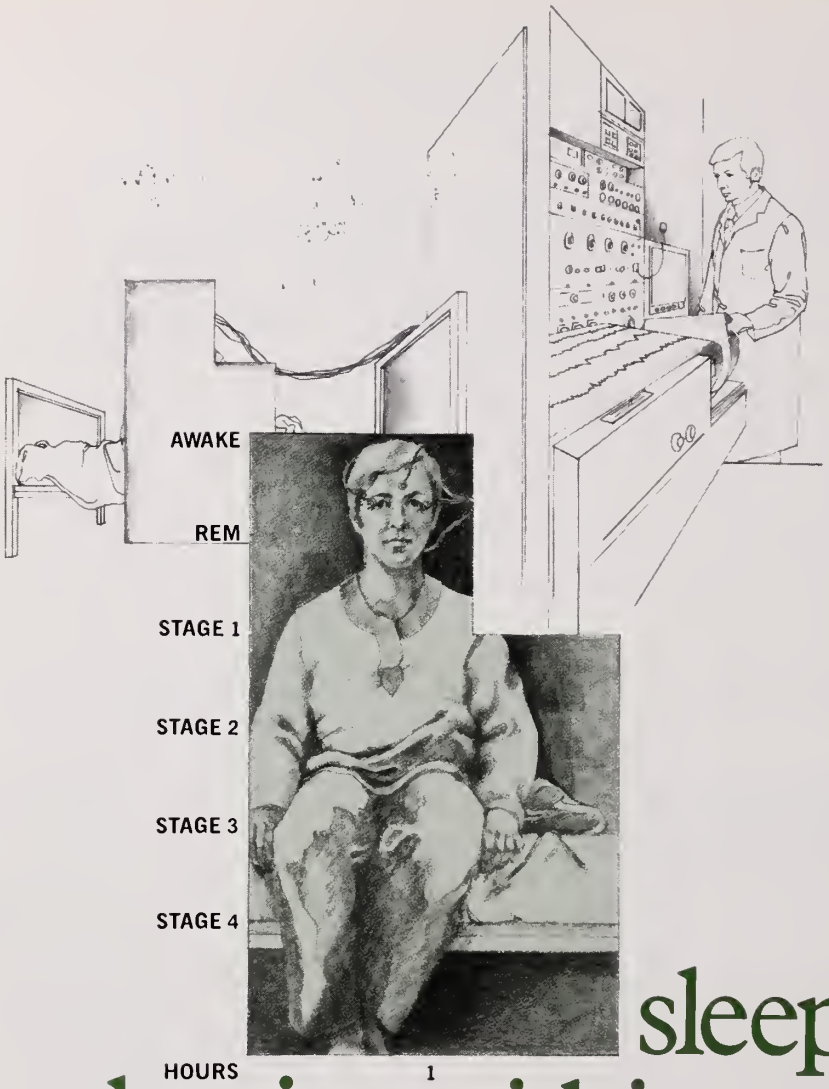
438 *Access to Medical Care as a Citizen's Right*

438 *Practical Criteria for the Diagnosis of Alcoholism in Hospital Practice*

440 *In Memoriam*

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII; OREGON; WASHINGTON, MONTANA, AND ALASKA**
(See Advertising Page 34)

01%-EXC 042674 SUB050400?8
EXCHANGE OFF
FRANCIS A COUNTWAY LIB
10 SHATTUCK
BOSTON



sleep begins within 17 minutes, on average...

an initial benefit of

Dalmane®

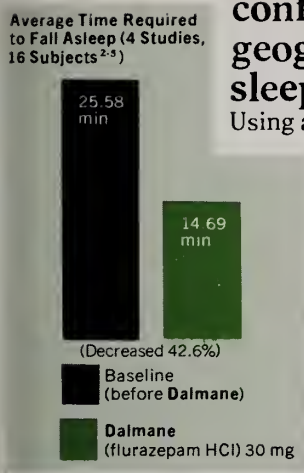
(flurazepam HCl)

proved by a 22-night clinical study of insomnia patients in the sleep research laboratory and at home[1]

Three insomnia patients selected for difficulty falling asleep were administered Dalmane (flurazepam HCl) 30 mg for 14 consecutive nights. Placebo was given for four nights prior to and four nights after Dalmane. Physiologic tracings on Dalmane nights 1-3 showed sleep induction time averaged 13.90 minutes; on Dalmane nights 12-14, 18.80 minutes. Combined average for the 6 monitored drug nights was 16.35 minutes.[1]

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON

MAY 21 1974



confirmed by clinical studies in four geographically separated sleep research laboratories[2-5]

Using a 14-night protocol involving eight insomniac and eight normal subjects, four studies confirmed the sleep-inducing effectiveness of Dalmane (flurazepam HCl) and the reproducibility of this response. On average, one 30-mg capsule induced sleep within 17 minutes. In all these studies, Dalmane induced sleep rapidly, reduced nighttime awakenings, and provided 7 to 8 hours of sleep without repeating dosage.[2-5]

Dalmane (flurazepam HCl) induces and maintains sleep, with relative safety

)almane is generally well tolerated; morning "hang-over" has been relatively ıfrequent. While dizziness, drowsiness, lightheadedness and the like have een noted most often, particularly in the elderly and debilitated, physicians hould be aware of the possibility of more serious reactions, as noted below.

efore prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, summary of which follows:

ıdications: Effective in all types of insomnia characterized by difficulty in falling asleep, equent nocturnal awakenings and/or early morning awakening; in patients with recurring ısomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful eep. Since insomnia is often transient and intermittent, prolonged administration is generally ɔt necessary or recommended.

ontraindications: Known hypersensitivity to flurazepam HCl.

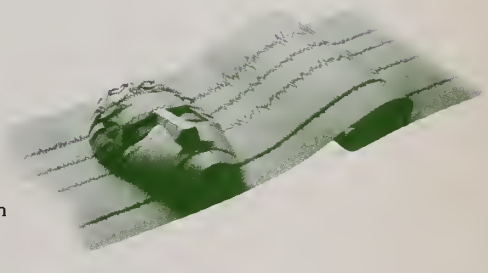
/arnings: Caution patients about possible combined effects with alcohol and other CNS epressants. Caution against hazardous occupations requiring complete mental alertness .g., operating machinery, driving). Use in women who are or may become pregnant only when ɔtential benefits have been weighed against possible hazards. Not recommended for use in ersons under 15 years of age. Though physical and psychological dependence have not been ported on recommended doses, use caution in administering to ddiction-prone individuals or those who might increase dosage.

recautions: In elderly and debilitated, initial dosage should be mited to 15 mg to preclude oversedation, dizziness and/or ataxia. combined with other drugs having hypnotic or CNS-depressant fects, consider potential additive effects. Employ usual precautions patients who are severely depressed, or with latent depression or ıicidal tendencies. Periodic blood counts and liver and kidney ınction tests are advised during repeated therapy. Observe usual recautions in presence of impaired renal or hepatic function.

dverse Reactions: Dizziness, drowsiness, lightheadedness, aggering, ataxia and falling have occurred, particularly in elderly debilitated patients. Severe sedation, lethargy, disorientation and ɔma, probably indicative of drug intolerance or overdosage, have een reported. Also reported were headache, heartburn, upset omach, nausea, vomiting, diarrhea, constipation, GI pain, nervous- ess, talkativeness, apprehension, irritability, weakness, palpitations, ıest pains, body and joint pains and GU complaints. There have so been rare occurrences of sweating, flushes, difficulty in focusing, urred vision, burning eyes, faintness, hypotension, shortness of eath, pruritus, skin rash, dry mouth, bitter taste, excessive saliva- on, anorexia, euphoria, depression, slurred speech, confusion, stlessness, hallucinations, and elevated SGOT, SGPT, total and rect bilirubins and alkaline phosphatase. Paradoxical reactions, g., excitement, stimulation and hyperactivity, have also been ported in rare instances.

osage: Individualize for maximum beneficial effect. *Adults:* 30 mg ual dosage; 15 mg may suffice in some patients. *Elderly or debil- ıted patients:* 15 mg initially until response is determined.

ıpplied: Capsules containing 15 mg or 30 mg flurazepam HCl.



when restful sleep is indicated

Dalmane®
(flurazepam HCl)

One 30-mg capsule *h.s.* — usual adult dosage (15 mg may suffice in some patients).
One 15-mg capsule *h.s.* — initial dosage for elderly or debilitated patients.

- **induces sleep within 17 minutes, on average**
- **reduces nighttime awakenings**
- **sustains sleep 7 to 8 hours, on average, without repeating dosage**

EFERENCES: 1. Kales A, *et al*: *Arch Gen Psychiatry 23*:226-232, Sep 1970
Karacan I, Williams RL, Smith JR: The sleep laboratory in the investigation of sleep and eep disturbances. Scientific exhibit at the 124th annual meeting of the American Psychiatric ssociation, Washington DC, May 3-7, 1971
Frost JD Jr: Data on file, Medical Department, Hoffmann-La Roche Inc, Nutley NJ
Vogel GW: Data on file, Medical Department, Hoffmann-La Roche Inc, Nutley NJ
Dement WC: Data on file, Medical Department, Hoffmann-La Roche Inc, Nutley NJ

ROCHE

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

IN GONORRHEA

INJECTION

Wycillin®

(STERILE PROCAINE PENICILLIN G SUSPENSION) WYETH

Gonorrhea, according to the national Center for Disease Control, is, if the parenteral route is chosen, most effectively treated with aqueous procaine penicillin G. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given at least 30 minutes prior to injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reaction.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported. (See "Warnings.")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated)—Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, preferably given at least 30 minutes prior to injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units. I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million units daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each TUBEX® disposable syringe 2,400,000 units (4-cc. size) contains procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.7% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. The multiple-dose 10-cc. vial contains per cc. 300,000 units procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. polyvinylpyrrolidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population.* And growing.

Among those in the 20-24 age-group, the incidence is even higher. And it, too, is growing.

In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

IN SYPHILIS

INJECTION

Bicillin® LONG-ACTING

(STERILE BENZATHINE PENICILLIN G SUSPENSION) WYETH

Syphilis is preferably treated with benzathine penicillin G, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular benzathine penicillin G.—Venereal infections: Syphilis, yaws, bejel and pinta.

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

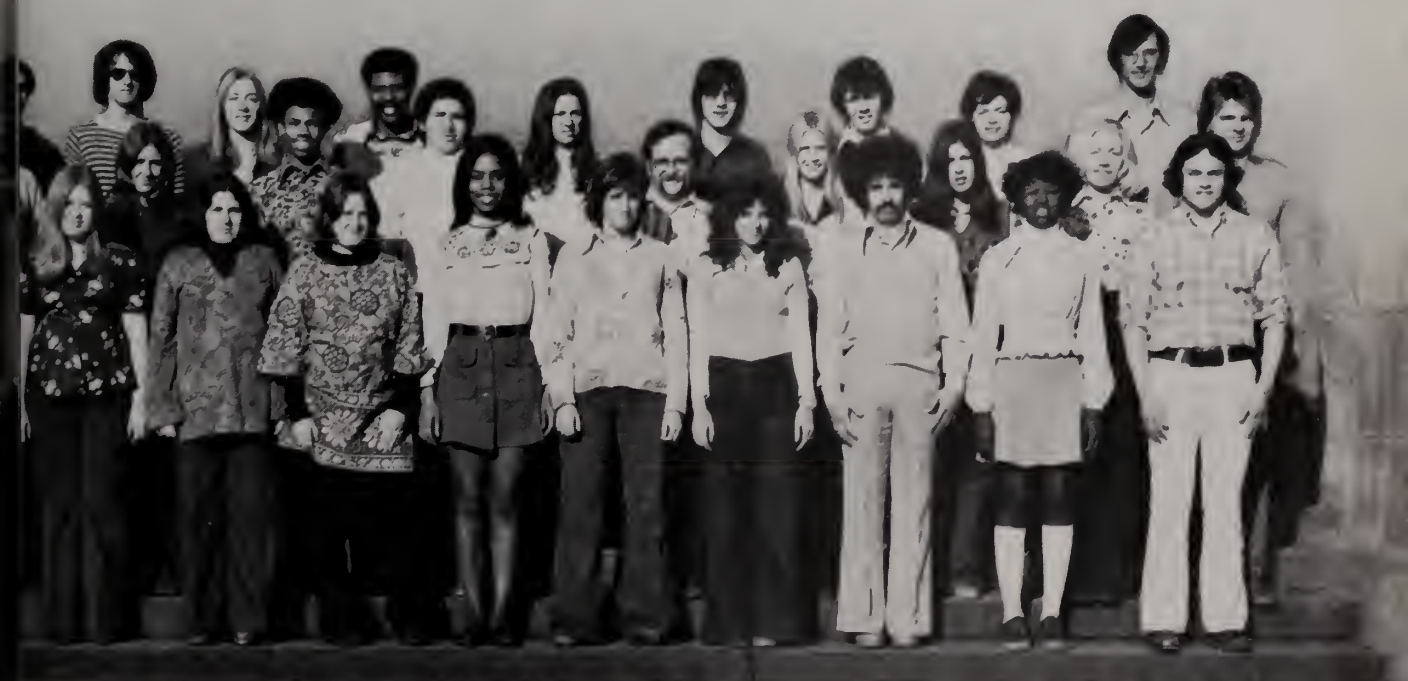
Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: 2,400,000 units in 4-cc. single dose disposable syringe. Each TUBEX disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. Units benzathine penicillin G (as active ingredient): 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. polyvinylpyrrolidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Wyeth Laboratories
Philadelphia, Pa. 19101



S. Dept. of Health, Education, and Welfare. VD Fact Sheet 1972. Publication No. (HSM) 73-8195.

THE WESTERN Journal of Medicine

Since 1902 • Formerly California Medicine

OWNED AND PUBLISHED BY THE CALIFORNIA MEDICAL ASSOCIATION
731 MARKET ST. • SAN FRANCISCO, CA 94103 • TELEPHONE (415) 777-2000

editorial communications to:
MALCOLM S. M. WATTS, M.D., *Editor*

business communications to:
LYTTON O. HETLAND, *Business Manager*

. . .

LLOYD H. SMITH, JR., M.D., *Associate Editor*
ROBERT F. EDWARDS, *Managing Editor*
DAVID GREER, *Associate Managing Editor*

Editorial Board

Chairman of the Board
Malcolm S. M. Watts, San Francisco

Allergy
Norman Shure, Los Angeles
Abba I. Terr, San Francisco

Anesthesiology
Ronald L. Katz, Los Angeles

Dermatology
George F. Odland, Seattle
Rees B. Rees, San Francisco
Richard B. Stoughton, La Jolla

General and Family Practice
Robert L. Hippen, San Diego
Herbert A. Holden, San Leandro

General Surgery
Frederick M. Anderson, Reno
Richard E. Gardner, San Francisco
Lucius D. Hill, Seattle

Industrial Medicine and Toxicology
Thomas H. Milby, Berkeley

Internal Medicine
Robert J. Bolt, Davis
J. David Bristow, Portland
Marcus A. Krupp, Palo Alto
Robert G. Petersdorf, Seattle
Donald W. Petit, Los Angeles
Edgar Wayburn, San Francisco
Nathan J. Zvaifler, San Diego

Neurology
Pierre M. Dreyfus, Davis
Robert A. Fishman, San Francisco
Phillip D. Swanson, Seattle

Obstetrics and Gynecology
Ralph C. Benson, Portland
William J. Dignam, Los Angeles
Ernest W. Page, San Francisco

Ophthalmology
David O. Harrington, San Francisco
Robert S. Hepler, Los Angeles

Orthopedics
Rodney K. Beals, Portland
John A. Blosser, Oakland
Paul E. McMaster, Beverly Hills

Otolaryngology
Mansfield F. W. Smith, San Jose
Paul H. Ward, Los Angeles

Pathology
Richard L. Kempson, Stanford
Averill A. Liebow, San Diego

Pediatrics
Robert E. Greenberg, Los Angeles
William L. Nyhan, San Diego
Henry R. Shinefield, San Francisco
Paul F. Wehrle, Los Angeles

Pharmacology
Sydney M. Finegold, Los Angeles
Kenneth L. Melmon, San Francisco

Physical Medicine and Rehabilitation
Elizabeth S. Austin, Los Angeles
Glenn G. Reynolds, San Jose

Plastic Surgery
Richard L. Dakin, San Rafael
N. John Wilde, Fresno

Psychiatry
Carl Eisdorfer, Seattle
Leon J. Epstein, San Francisco
George L. Mallory, Los Angeles
Helen Tausend, Los Angeles

Public Health
J. M. Stubblebine, Sacramento
Irma M. West, Sacramento

Radiology
H. Joachim Burhenne, San Francisco
Robert B. Engle, Pasadena
Melvin M. Figley, Seattle

Thoracic and Cardiac Surgery
John E. Connolly, Irvine
Albert Starr, Portland

Urology
Thomas F. Conroy, San Mateo
Ruben F. Gittes, La Jolla

Consultants in Medical Services and Health Care
Gerald A. Besson, Sunnyvale
Paul Scholten, San Francisco

Policy Committee—Editorial Board

Stanley A. Moore ..... San Diego
Carl Goetsch ..... Berkeley
Joseph F. Boyle ..... Los Angeles
Henry V. Eastman ..... Tustin
E. Kash Rose ..... Napa
Albert G. Clark ..... San Francisco
Malcolm S. M. Watts ..... San Francisco

Advertisements—The Western Journal of Medicine is published the first week of each month. Advertising copy must be received not later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee.

SALES REPRESENTATIVES: John H. Harling, Inc.

EAST:
Saul Hornik
655 Amboy Avenue
Woodbridge, N.J. 07095
Tel. (201) 636-7150

MIDWEST:
John Harling • James Anton
18 So. Michigan Ave.
Chicago, Ill. 60603
Tel. (312) 641-0755

WEST: Melvin B. Tyler
731 Market St.
San Francisco, Ca. 94103
Tel. (415) 777-2000

Copyright, 1974, by the California Medical Association.

All material subject to this copyright appearing in The Western Journal of Medicine may be photocopied for the non-commercial purpose of scientific or educational advancement.

Subscription prices, $8 ($9 for foreign countries); student subscription $4; single copies 80 cents.

Volumes begin with the first of January and the first of July. Subscriptions may commence at any time.

Change of Address—Requests for change of address should give both the old and new address.

Contributions of Scientific and Original Articles

Responsibilities for Statements and Conclusions in Original Articles—Authors are responsible for all statements, conclusions and methods of presenting their subjects. These may or may not be in harmony with the views of the editorial staff. It is aimed to permit authors to have as wide latitude as the general policy of the Journal and the demands on its space may permit. The right to reduce, revise or reject any manuscript is always reserved.

Exclusive Publication—Articles are accepted for publication on condition that they are contributed solely to this Journal. Ordinarily contributors will be notified within 60 days if a manuscript is accepted for publication. Every effort will be made to return unused manuscripts.

Length of Articles—Ordinarily articles should not exceed 3,000 words (approximately 5 printed pages). Under exceptional circumstances only will articles of over 4,000 words be published.

Manuscripts—Manuscripts should be typewritten, double spaced and the original typescript plus one copy submitted.

Illustrations—Ordinarily publication of 2 or 3 illustrations accompanying an article will be paid for by The Western Journal of Medicine. Any number beyond this might have to be paid for by the author.

References—Should conform to the following order: name of author, title of article, name of periodical, with volume, inclusive pages, month and year—i.e.: Lee GS: The heart rhythm following therapy with digitalis—In theory and practice. Arch Int Med 44:554-562, Dec 1942. They should be listed in the order in which they are cited in the text, numbered in sequence and punctuated as above.

Reprints—Reprints must be paid for by the author at established standard rates.

Contributions of "Letters to the Editor"

The Editorial Board will be glad to receive and consider for publication letters containing information of general interest to physicians or presenting constructive criticisms on issues of the day.

"Entered as second class matter at the post office in San Francisco and additional mailing offices under the Act of March 3, 1879." Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized August 10, 1918.

first came the
ANTIHISTAMINES
and the
PHENOTHIAZINES

and now...

a NEW effective antinausean for use in anest

Chemically unique

Emete-con (benzquinamide HCl) is chemically unrelated to the phenothiazines and to other anti-emetics. It is a non-amine-depleting benzoquinolizine derivative.

Effective

Efficacy comparable to a standard phenothiazine, demonstrated in well-control clinical studies.*

on-phenothiazine
ntiemetic
sia and surgery

Well tolerated
Drowsiness appears to be the most common reaction. Other more significant reactions have been reported; please refer to the package insert.

New
Emete-con™
(benzquinamide HCl) IM/IV

Usual adult dose: IM-50 mg., IV-25 mg.

For prescribing information, including adverse reactions and contraindications, please see following page.

Roerig introduces NEW

Emete-con™ (benzquinamide HCl)IM/IV

PRESCRIBING INFORMATION
Emete-con™ (Benzquinamide-Hydrochloride)
For Intramuscular and Intravenous Use

Description. Benzquinamide is a non-amine-depleting benzoquinolizine derivative, chemically unrelated to the phenothiazines and to other antiemetics.

Chemically, Emete-con (benzquinamide-hydrochloride) is N, N-diethyl-1,3,4,6,7,11b-hexahydro-2-hydroxy-9, 10-dimethoxy-2H-benzo(a)quinolizine-3-carboxamide acetate hydrochloride. The empirical formula is $C_{22}H_{32}N_2O_5$. HCl and the molecular weight is 441.

Emete-con for injection contains: Benzquinamide HCl equivalent to benzquinamide 50 mg/vial and citric acid 1%. When reconstituted with 2.2 ml of sterile water for injection, each vial yields 2 ml of a solution containing benzquinamide, 25 mg/ml. When reconstituted, this product maintains its potency for 14 days at room temperature. DO NOT REFRIGERATE.

Actions. Benzquinamide HCl exhibited antiemetic, antihistaminic, mild anticholinergic and sedative action in animals. Studies conducted in dogs and human volunteers have demonstrated suppression of apomorphine-induced vomiting; however, relevance to clinical efficacy has not been established. The mechanism of action in humans is unknown. The onset of antiemetic activity in humans usually occurs within 15 minutes.

Benzquinamide metabolism has been studied in animals and in man. In both species, 5-10% of an administered dose is excreted unchanged in the urine. The remaining drug undergoes metabolic transformation in the liver by at least three pathways to a spectrum of metabolites which are excreted in the urine and in the bile, from which the more polar metabolites are not reabsorbed but are excreted in the feces. The half-life in plasma of Emete-con is about 40 minutes. More than 95% of an administered dose was excreted within 72 hours in animal studies using C14-labeled benzquinamide. In blood, benzquinamide is about 58% bound to plasma protein.

Indications. Emete-con is indicated for the prevention and treatment of nausea and vomiting associated with anesthesia and surgery.

Since the incidence of postoperative and postanesthetic vomiting has decreased with the adoption of modern techniques and agents, the prophylactic use of Emete-con should be restricted to those patients in whom emesis would endanger the results of surgery or result in harm to the patient.

Contraindications. Emete-con is contraindicated in individuals who have demonstrated hypersensitivity to the drug.

Warnings. *Use in Pregnancy:* No teratogenic effects of benzquinamide were demonstrated in reproduction studies in chick embryos, mice, rats and rabbits. The relevance of these data to the human is not known. However, safe use of this drug in pregnancy has not been established and its use in pregnancy is not recommended.

Use in Children: As the data available at present are insufficient to establish proper dosage in children, the use of Emete-con in children is not recommended.

Introvenous use: Sudden increase in blood pressure and transient arrhythmias (premature ventricular and auricular contractions) have been reported following intravenous administration of benzquinamide. Until a more predictable pattern of the effect of intravenous benzquinamide has been established, the intramuscular route of administration is considered preferable. The intravenous route of administration should be restricted to patients without cardiovascular disease and receiving no pre-anesthetic and/or concomitant cardiovascular drugs.

Precautions. Benzquinamide, like other antiemetics, may mask signs of overdosage of toxic drugs or may obscure diagnosis of such conditions as intestinal obstruction and brain tumor.

Adverse Reactions. The following adverse reactions have been reported in subjects who have received benzquinamide. Because of the multiplicity of medications commonly used in the practice of anesthesia, unequivocal relationship to a specific drug administered usually cannot be established. However, drowsiness appears to be the most common reaction. One case of pronounced allergic reaction has been encountered, characterized by pyrexia and urticaria.

System Affected—*Autonomic Nervous System:* Dry mouth, shivering, sweating, hiccoughs, flushing, salivation, blurred vision.

Cardiovascular System: Hypertension, hypotension, dizziness, atrial fibrillation, premature auricular and ventricular contractions.

Central Nervous System: Drowsiness, insomnia, restlessness, headache, excitement, nervousness.

Gastrointestinal System: Anorexia, nausea.

Musculoskeletal System: Twitching, shaking/tremors, weakness.

Skin: Hives/rash.

Other Systems: Fatigue, chills, increased temperature.

Dosage and Administration. *Intramuscular:* 50 mg (0.5 mg/kg–1.0 mg/kg)

First dose may be repeated in one hour with subsequent doses every 3-4 hours, as necessary. The precautions applicable to all intramuscular injections should be observed. Emete-con should be injected well within the mass of a larger muscle. The deltoid area should be used only if well developed. Injections should not be made into the lower and mid-thirds of the upper arm. Aspiration of the syringe should be carried out to avoid inadvertent intravascular injection.

Therapeutic blood levels and demonstrable antiemetic activity appear within fifteen minutes of intramuscular administration. When the objective of therapy is the prevention of nausea and vomiting, intramuscular administration is recommended at least fifteen minutes prior to emergence from anesthesia.

Introvenous: 25 mg (0.2 mg/kg–0.4 mg/kg as a single dose) administered slowly (1 ml per 0.5 to 1 minute). Subsequent doses should be given intramuscularly.

The intravenous route of administration should be restricted to patients without cardiovascular disease (See WARNINGS). If it is necessary to use Emete-con intravenously in elderly or debilitated patients, benzquinamide should be administered cautiously and the lower dose range is recommended.

This preparation must be initially reconstituted with 2.2 ml of sterile water. This procedure yields 2 ml of a solution equivalent to 25 mg benzquinamide/ml, which maintains its potency for 14 days at room temperature.
DO NOT REFRIGERATE.

Overdosage. *Manifestotions:* On the basis of acute animal toxicology studies, gross Emete-con overdosage in humans might be expected to manifest itself as a combination of Central Nervous System stimulant and depressant effects. This speculation is derived from experimental studies in which intravenous doses of benzquinamide, at least 150 times the human therapeutic dose, were administered to dogs.

Treatment: There is no specific antidote for Emete-con overdosage. General supportive measures should be instituted, as indicated. Atropine may be helpful. Although there has been no direct experience with dialysis, it is not likely to be of value, since benzquinamide is extensively bound to plasma protein.

How Supplied. Emete-con for IM/IV use is available in a vial containing benzquinamide HCl equivalent to 50 mg of benzquinamide in packages of 10 vials.

Caution. Federal law prohibits dispensing without prescription.

Bibliography

Zauder, H.L., et al.: Prophylaxis of Postoperative Emesis, Scientific Exhibit presented at 122nd Annual Convention of the A.M.A., June 23-27, 1973.

Lutz, H., and Immich, H.: Antiemetic effect of benzquinamide in postoperative vomiting. Curr Ther. Res. 14:178, April, 1972.

Finn, H., et al.: Antiemetic efficacy of benzquinamide. N.Y. J. Med. 71:61, March 15, 1971.

Larrauri, R.M.: Benzquinamide parenteral for the treatment of post-operative nausea and vomiting. Curr. Ther. Res. 11:65, March, 1969.

ROERIG Pfizer

A division of Pfizer Pharmaceuticals
New York, New York 10017

New Emete-con™ (benzquinamide HCl)IM/IV

Each vial contains benzquinamide hydrochloride equivalent to 50 mg. of benzquinamide with 0.45 mg. of citric acid.

When a cough spoils your patient's day...

Triaminic® Expectorant

Each teaspoonful (5 ml.) contains:
Triaminic, 25 mg. (phenylpropanolamine hydrochloride, 12.5 mg.; pheniramine maleate, 6.25 mg.; pyrilamine maleate, 6.25 mg.); glyceryl guaiacolate, 100 mg.; alcohol, 5%.

Triaminic® Expectorant with Codeine ©V

Each teaspoonful (5 ml.) contains:
Codeine phosphate, 10 mg. (Warning: May be habit forming); Triaminic, 25 mg. (phenylpropanolamine hydrochloride, 12.5 mg.; pheniramine maleate, 6.25 mg.; pyrilamine maleate, 6.25 mg.); glyceryl guaiacolate, 100 mg.; alcohol, 5%.
Triaminic Expectorant with Codeine is a Schedule V controlled substance.

The Adult Expectorants that are great for kids, too.

Dorsey Laboratories/Division of Sandoz-Wander, Inc./Lincoln, Nebraska 68501

B--RB

Tofranil-PM®

imipramine pamoate

Capsules* of 150, 125, 100 and 75 mg.

Provides the therapeutic effectiveness of divided daily doses with no loss of safety.

*Each capsule contains imipramine pamoate equivalent to 150, 125, 100 or 75 mg. of imipramine hydrochloride.

ne dose lasts from bedtime to bedtime.

single-dose therapy in depression
en the dosage is established.

r many patients, the 150-mg. capsule
ay be the most effective single
aily dose.

ay markedly reduce the probability
f missed doses.

ffers dosage convenience that
ssures greater patient cooperation.

ecomes part of the regular bedtime
utine—making it easier to establish
more reliable pattern of self-med-
ation.

- offers the therapeutic equivalency of divided daily doses of Tofranil®, imipramine hydrochloride, with no loss of efficacy or safety.
- has the convenience and flexibility of a full range of single daily dosage strengths.
- saves time and cost of dosage administration in the hospital.

Please read the prescribing information for details of usage, precautions, warnings, contraindications, adverse experiences, and dosage recommendations. A summary appears on the following page.

Tofranil-PM® Geigy
imipramine pamoate

Capsules* of 150, 125, 100 and 75 mg.

*Each capsule contains imipramine pamoate equivalent to 150, 125, 100 or 75 mg. of imipramine hydrochloride.

One dose lasts from bedtime to bedtime.

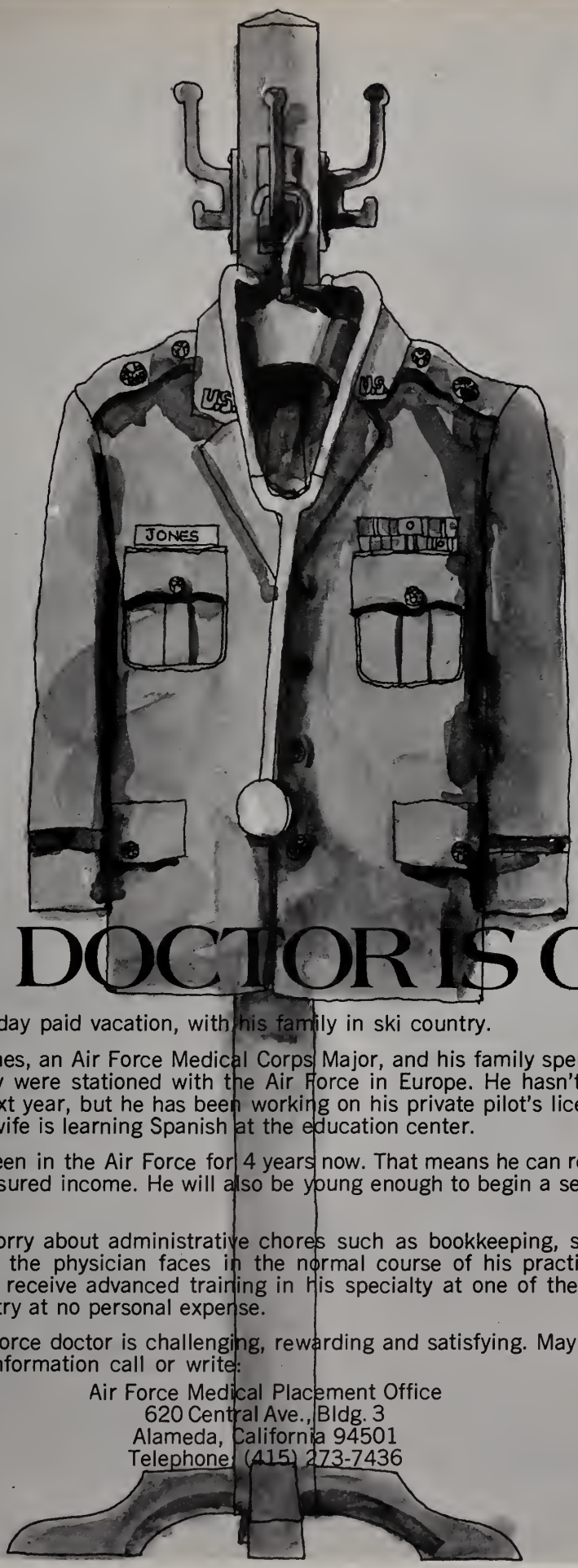
Tofranil-PM®
brand of imipramine pamoate
Tofranil®
brand of imipramine hydrochloride USP

Indications: For the relief of symptoms of depression. Endogenous depression is more likely to be alleviated than other depressive states.
Contraindications: The concomitant use of monoamine oxidase inhibiting compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur in patients receiving such combinations. The potentiation of adverse effects can be serious, or even fatal. When it is desired to substitute Tofranil, brand of imipramine hydrochloride, in patients receiving a monoamine oxidase inhibitor, as long an interval should elapse as the clinical situation will allow, with a minimum of 14 days. Initial dosage should be low and increases should be gradual and cautiously prescribed. The drug is contraindicated during the acute recovery period after a myocardial infarction. Patients with a known hypersensitivity to this compound should not be given the drug. The possibility of cross-sensitivity to other dibenzazepine compounds should be kept in mind.
Warnings: *Usage in Pregnancy:* Safe use of imipramine during pregnancy and lactation has not been established; therefore, in administering the drug to pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards. Animal reproduction studies have yielded inconclusive results. There have been clinical reports of congenital malformation associated with the use of this drug, but a causal relationship has not been confirmed.
Extreme caution should be used when this drug is given to:
- patients with cardiovascular disease because of the possibility of conduction defects, arrhythmias, myocardial infarction, strokes and tachycardia;
- patients with increased intraocular pressure, history of urinary retention, or history of narrow-angle glaucoma because of the drug's anticholinergic properties;
- hyperthyroid patients or those on thyroid medication because of the possibility of cardiovascular toxicity;
- patients with a history of seizure disorder because this drug has been shown to lower the seizure threshold;
- patients receiving guanethidine or similar agents since imipramine may block the pharmacologic effects of these drugs.

Usage in Children: Pending evaluation of results from clinical trials in children, Tofranil, brand of imipramine hydrochloride, is not recommended for treatment of depression in patients under twelve years of age.
Tofranil-PM, brand of imipramine pamoate, should not be used in children of any age because of the increased potential for acute overdosage due to the high unit potency (75 mg., 100 mg., 125 mg. and 150 mg.). Each capsule contains imipramine pamoate equivalent to 75 mg., 100 mg., 125 mg. or 150 mg. imipramine hydrochloride.
Since imipramine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as operating an automobile or machinery, the patient should be cautioned accordingly.
Precautions: It should be kept in mind that the possibility of suicide in seriously depressed patients is inherent in the illness and may persist until significant remission occurs. Such patients should be carefully supervised during the early phase of treatment with Tofranil, brand of imipramine hydrochloride, and may require hospitalization. Prescriptions should be written for the smallest amount feasible.
Hypomanic or manic episodes may occur, particularly in patients with cyclic disorders. Such reactions may necessitate discontinuation of the drug. If needed, Tofranil, brand of imipramine hydrochloride, may be resumed in lower dosage when these episodes are relieved. Administration of a tranquilizer may be useful in controlling such episodes.
Prior to elective surgery, imipramine hydrochloride should be discontinued for as long as the clinical situation will allow.
An activation of the psychosis may occasionally be observed in schizophrenic patients and may require reduction of dosage and the addition of a phenothiazine.
In occasional susceptible patients or in those receiving anticholinergic drugs (including antiparkinsonism agents) in addition, the atropine-like effects may become more pronounced (e.g., paralytic ileus). Close supervision and careful adjustment of dosage is required when this drug is administered concomitantly with anticholinergic or sympathomimetic drugs.
Avoid the use of preparations, such as decongestants and local anesthetics, which contain any sympathomimetic amine (e.g., adrenalin, noradrenalin), since it has been reported that tricyclic antidepressants can potentiate the effects of catecholamines.
Patients should be warned that the concomitant use of alcoholic beverages may be associated with exaggerated effects.
Both elevation and lowering of blood sugar levels have been reported.
Concurrent administration of imipramine with electroshock therapy may increase the hazards; such treatment should be limited to those patients for whom it is essential, since there is limited clinical experience.
Adverse Reactions: Note: Although the listing which follows includes a few adverse reactions which have not been reported with this specific drug, the pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when imipramine is administered.
Cardiovascular: Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke, falls.
Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.
Neurological: Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alterations in EEG patterns; tinnitus.
Anticholinergic: Dry mouth, and, rarely, associated sublingual adenitis, blurred vision, disturbances of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.
Allergic: Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue); drug fever; cross-sensitivity with desipramine.
Hematologic: Bone marrow depression including agranulocytosis; eosinophilia; purpura; thrombocytopenia. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathological neutrophil depression.
Gastrointestinal: Nausea and vomiting, anorexia, epigastric distress, diarrhea; peculiar taste, stomatitis, abdominal cramps, black tongue.
Endocrine: Gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels.
Other: Jaundice (simulating obstructive); altered liver function; weight gain or loss; perspiration; flushing, urinary frequency; drowsiness, dizziness, weakness and fatigue; headache; parotid swelling; alopecia.
Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache and malaise.
Dosage and Administration: Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients as compared to hospitalized patients who will be under close supervision. Dosage should be initiated with Tofranil, brand of imipramine hydrochloride, at a low level and increased gradually, noting carefully the clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a longer period of time, at the lowest dose that will maintain remission.
Once-a-day maintenance dosage can be provided with Tofranil-PM, brand of imipramine pamoate, capsules if this dosage has been established as explained above. This dose may be given at bedtime. For the occasional patient who manifests stimulation and insomnia with this dosage regimen, the capsules may be given in the morning.
Parenteral administration should be used only for starting therapy in patients unable or unwilling to use oral medication. The oral form should supplant the injectable as soon as possible.
How Supplied: Tofranil, brand of imipramine hydrochloride: Round tablets of 25 and 50 mg.; triangular tablets of 10 mg.; and ampuls, each containing 25 mg. in 2 cc. for I.M. administration.
Tofranil-PM, brand of imipramine pamoate: Capsules of 75, 100, 125 and 150 mg. (Each capsule contains imipramine pamoate equivalent to 75, 100, 125 or 150 mg. of imipramine hydrochloride.) (B) 98-146-850-P (2/74)

For complete details, including dosage and administration, please refer to the full prescribing information.

GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502



THE DOCTOR IS OUT

He's enjoying a 30 day paid vacation, with his family in ski country.

Last year Doctor Jones, an Air Force Medical Corps Major, and his family spent their vacation in Switzerland. They were stationed with the Air Force in Europe. He hasn't said what they have planned for next year, but he has been working on his private pilot's license at the base flying club and his wife is learning Spanish at the education center.

Doctor Jones has been in the Air Force for 4 years now. That means he can retire in less than 16 years with an assured income. He will also be young enough to begin a second successful career.

He won't have to worry about administrative chores such as bookkeeping, supplies, rent or the other problems the physician faces in the normal course of his practice. And he was recently selected to receive advanced training in his specialty at one of the finest research centers in the country at no personal expense.

The life of the Air Force doctor is challenging, rewarding and satisfying. Maybe it's your kind of life? For more information call or write:

Air Force Medical Placement Office
620 Central Ave., Bldg. 3
Alameda, California 94501
Telephone: (415) 273-7436

What's on your patient's face...

may be more important than his chief complaint

Patient P.T.* seen on 3/29/67 shows typical lesions of moderately severe keratoses. Note residual scarring on ridge of nose from previous cryosurgical and electrosurgical procedures.

Patient P.T.* seen on 6/12/67, seven weeks after discontinuation of 5% FU cream. Reaction has subsided. Residual scarring not seen except that due to prior surgery. Inflammation has cleared and face is clear of keratotic lesions.

*Data on file, Hoffmann-La Roche Inc., Nutley, N.J

The lesions on his face are solar/actinic— so-called "senile" keratoses... and they may be premalignant.

Solar, actinic or senile keratoses

These lesions may be called by several names, but they usually can be identified by the following characteristics. The typical lesion is flat or slightly elevated, of a brownish or reddish color, papular, dry, rough, adherent and sharply defined. They commonly occur as multiple lesions, chiefly on the exposed portions of the skin.

Sequence of therapy— selectivity of response

After several days of therapy with Efudex® (fluorouracil), erythema may begin to appear in the area of the lesions; this reaction usually reaches its height of unsightliness and discomfort within two weeks, declining after discontinuation of therapy. This reaction occurs in affected areas. Since the response is so predictable, lesions that do not respond should be biopsied.

Acceptable results

Treatment with Efudex provides highly favorable cosmetic results. Incidence of scarring is low. This is particularly important with multiple facial lesions. Efudex should be applied with care near the eyes, nose and mouth.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Multiple actinic or solar keratoses.

Contraindications: Patients with known hypersensitivity to any of its components.

Warnings: If occlusive dressing used, may increase inflammatory reactions in adjacent normal skin. Avoid prolonged exposure to ultraviolet rays. Safe use in pregnancy not established.

Precautions: If applied with fingers, wash hands immediately. Apply with care near eyes, nose and mouth. Lesions failing to respond or recurring should be biopsied.

Adverse Reactions: Local—pain, pruritus, hyperpigmentation and burning at application site most frequent; also dermatitis, scarring, soreness and tenderness. Also reported—insomnia, stomatitis, suppuration, scaling, swelling, irritability, medicinal taste, photosensitivity, lacrimation, leukocytosis, thrombocytopenia, toxic granulation and eosinophilia.

Dosage and Administration: Apply sufficient quantity to cover lesion twice daily with nonmetal applicator or suitable glove. Usual duration of therapy is 2 to 4 weeks.

How Supplied: Solution, 10-ml drop dispensers—containing 2% or 5% fluorouracil on a weight/weight basis, compounded with propylene glycol, tris(hydroxymethyl)-aminomethane, hydroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate.

Cream, 25-Gm tubes—containing 5% fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

This patient's lesions were resolved with

Efudex®

fluorouracil/Roche®

5% cream/solution...a Roche exclusive

When the asthmatic can anticipate the attack

Bronkotabs®

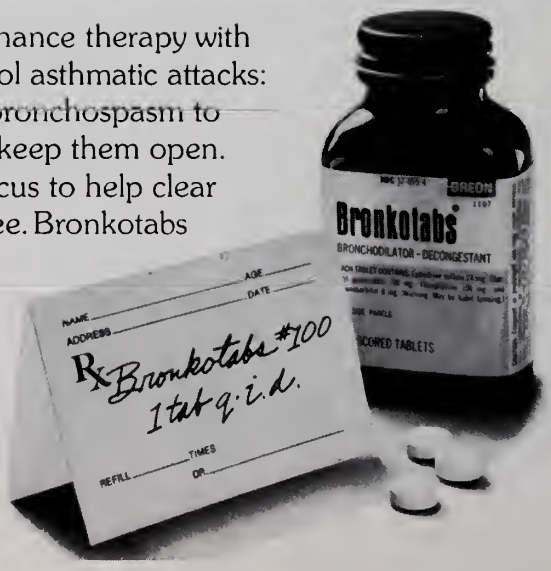
Each tablet contains ephedrine sulfate 24 mg; theophylline 100 mg; glyceryl guaiacolate 100 mg; phenobarbital 8 mg (warning: may be habit-forming).

can help forestall or relieve it

Why day to day maintenance therapy with Bronkotabs helps control asthmatic attacks:

Bronkotabs relieves bronchospasm to open airways and help keep them open.

Bronkotabs thins mucus to help clear the tracheobronchial tree. Bronkotabs decongests bronchiolar mucosa to improve the passage of air. Economical long-term therapy.



PRECAUTIONS AND ADVERSE EFFECTS: Sympathomimetic side effects are minimal, and there are none of the dangers or side effects associated with steroid therapy. However, frequent or prolonged use may cause nervousness, restlessness or sleeplessness. Should be used with caution in the presence of hypertension, heart disease or hyperthyroidism. Drowsiness may occur. Ephedrine may cause urinary retention, especially in the presence of partial obstruction, as in prostatism.

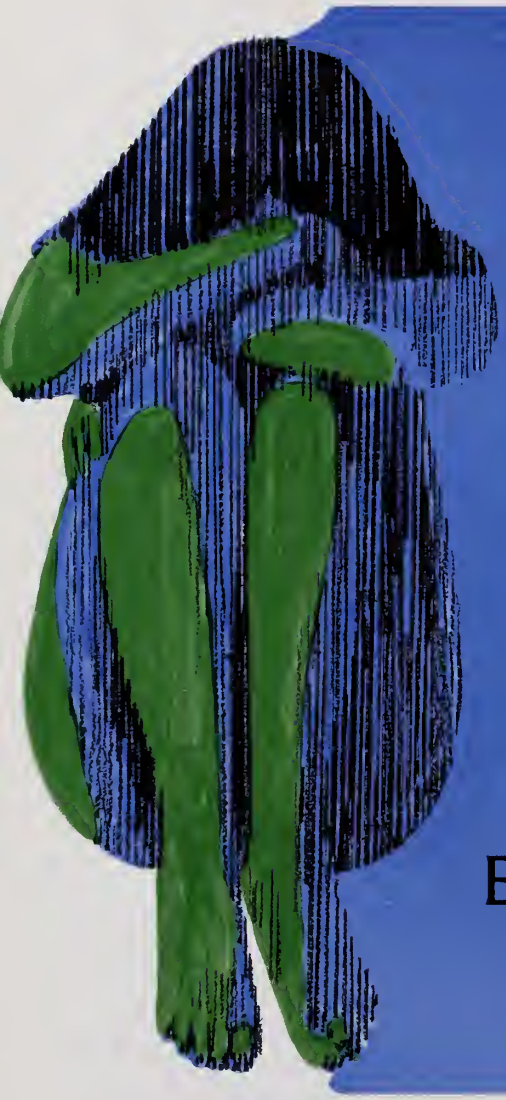
DOSAGE: Adults, one tablet every three or four hours, four or five times daily. Children over six, one-half the adult dose. Children under six, as directed.

SUPPLIED: Bottles of 100 and 1,000 tablets.

BREON

BREON LABORATORIES INC.
90 Park Avenue, New York, N.Y. 10016

When you see anxiety-look for depression
NORPRAMIN®
(desipramine hydrochloride)



when depression is primary

NORPRAMIN®
(desipramine hydrochloride)

HELPS PROVIDE EARLY CONTROL OF DEPRESSIVE SYMPTOMS...

Anxiety is an invidious symptom. It feeds upon sickness, gnaws, grows and invades every cranny of psychic pathology adding intensity to torment. Anxiety as a symptom secondary to depression may be so dominant that it obscures the primary diagnosis. It may suggest treatment with tranquilizers which often help. But as the vampire of legend had to have a laurel stake driven through its heart to truly die, so anxiety secondary to depression will not cease to nibble and bite until an antidepressant eradicates the primary illness—and symptomatic anxiety starves.

IN BRIEF:

Indications: Norpramin® (desipramine hydrochloride) is indicated for the relief of depressive symptoms. Endogenous depressions are more likely to be alleviated than others.

Contraindications: Desipramine hydrochloride should not be given within two weeks of treatment with a monoamine oxidase inhibitor. Contraindications include the acute recovery period following myocardial infarction and hypersensitivity to the drug. Cross sensitivity with other dibenzazepines is a possibility.

Warnings: 1. Extreme caution should be used in patients: (a) with cardiovascular disease, (b) with a history of urinary retention or glaucoma, (c) with thyroid disease or those on thyroid medication, (d) with a history of seizure disorder. 2. This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds. 3. *Use in Pregnancy:* Safe use during pregnancy and lactation has not been established. 4. *Use in Children:* Norpramin® (desipramine hydrochloride) is not recommended for use in children. 5. This drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Therefore, the patient should be cautioned accordingly.

Precautions: This drug should be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with drugs of this class. If possible, dispense in child-resistant containers. It should be kept out of reach of children. Reduce dosage, or alter treatment, if serious adverse effects occur. Norpramin® (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state alter the depressive phase terminates and may cause exacerbation of phychosis in schizophrenic patients. Use cautiously with anticholinergic or sympathomimetic drugs. Response to alcoholic beverages may be exaggerated. In the concurrent administration of ECT and antidepressant drugs one should consider the possibility of increased risk relative to benefits. Discontinue as soon as possible prior to elective surgery because of possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients on desipramine hydrochloride. Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is neutropenia.

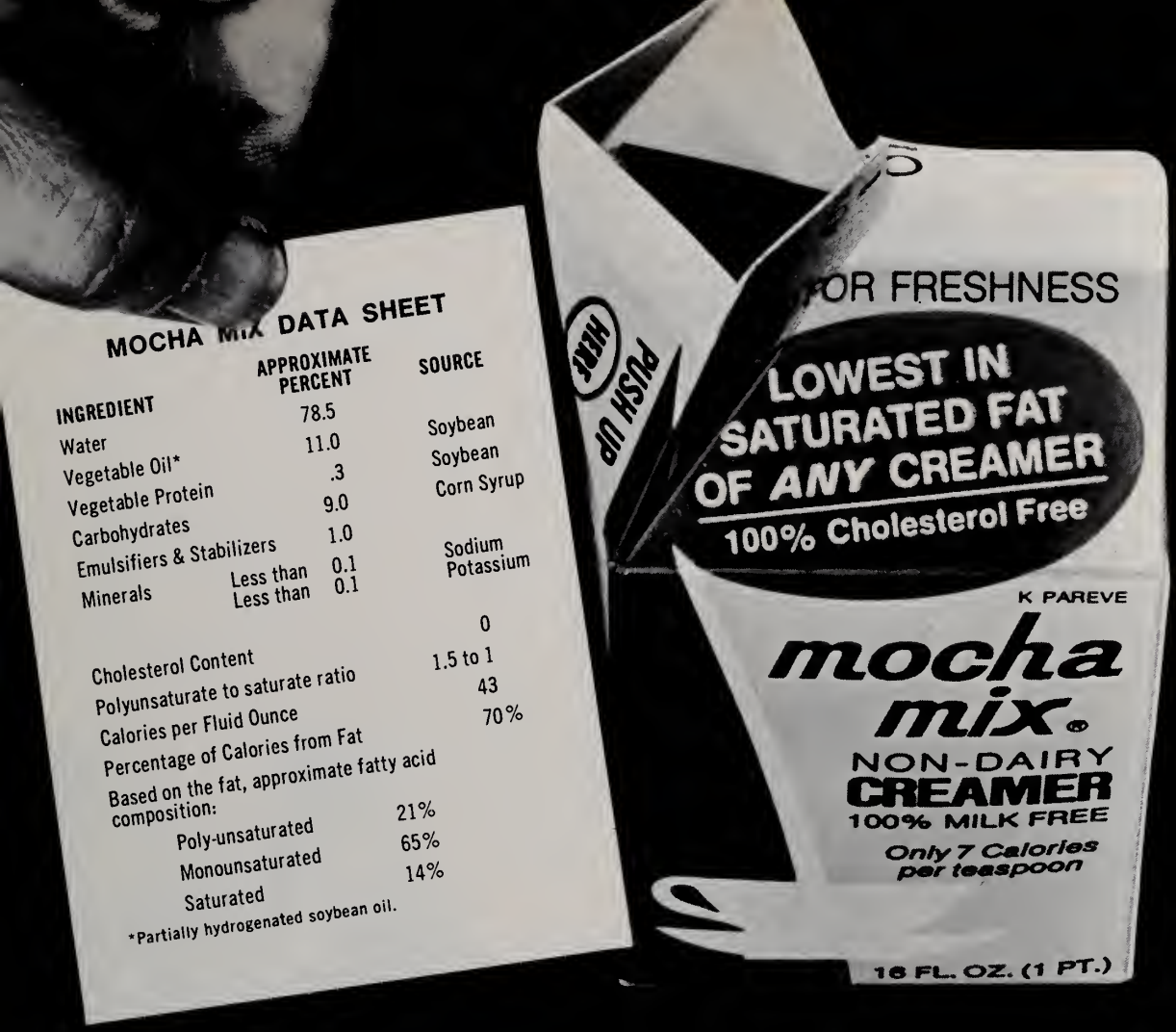
Adverse Reactions: *Cardiovascular:* hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke. *Psychiatric:* confusional states (especially in the elderly), hallucinations, disorientation, delusions; anxiety, agitation; insomnia and nightmares; hypomania; exacerbation of phychosis. *Neurological* paresthesias of extremities; incoordination, ataxia, tremors, peripheral nauropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus. *Anticholinergic:* dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, hypotonic bladder. *Allergic:* skin rash, petechiae, urticaria, itching, photosensitization, edema (of face and tongue or general), drug fever. *Hematologic:* agranulocytosis, eosinophilia, purpura, thrombocytopenia. *Gastrointestinal:* anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue. *Endocrine:* gynecomastia; breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, testicular swelling; elevation or depression of blood sugar levels. *Other:* jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia. *Withdrawal Symptoms:* Though not indicative of addiction, abrupt cessation after prolonged therapy may produce nausea, headache and malaise.

Dosage and Administration: *The usual adult dose:* 50 mg. three times daily; increase if necessary after 7 to 10 days to maximum of 200 mg. daily. Dosages above 200 mg. per day are not recommended. *Maintenance:* At a lower dose adequate to maintain remission. *Adolescent and geriatric patient dose:* 25 to 50 mg. daily if necessary.

Overdosage: There is no specific antidote for desipramine, nor are there specific phenomena of diagnostic value characterizing poisoning by the drug. The principles of management of coma and shock by means of the mechanical respirator, cardiac pacemaker, monitoring of central venous pressure and regulation of fluid- and acid-base balance are well known in most medical centers. If heart failure is imminent, digitalize promptly.

Manufactured by LAKESIDE LABORATORIES
Division of Colgate-Palmolive Company

Distributed by
LAKESIDE LABORATORIES, INC.
Milwaukee Wisconsin 53201



Mocha Mix® presents its credentials:

Study them. Note how low Mocha Mix® is in saturated fat. (Actually the lowest of any creamer — liquid, frozen or powdered.) Then note the unsaturated to saturated fat ratio (1.5:1). And Mocha Mix is 100% milk-free and 100% cholesterol-free, too! Taste? In coffee . . . on cereal, fruit or desserts . . . or for cooking, any way, any time a creamer is called for, Mocha Mix is the most delicious creamer ever!

In addition to the 16 oz. size found in the dairy case of most grocery stores, Mocha Mix is available in larger sizes and ½ oz. portion packs for hospitals and institutions.

Interested? Send us a note and we will send you a supply of coupons your patients can redeem at their grocers. Hospital service may also be supplied upon request. Mail to: Mocha Mix Dept. Presto Food Products, Inc. P.O. Box No. 21908, Los Angeles, Calif. 90021

***mocha mix*. . . . the non-dairy creamer that's lowest in saturated fat!**

to help treat what you often find:
obvious moderate to severe anxiety
with a less obvious underlying depression

TRIAVIL®

containing perphenazine and amitriptyline HCl

a tranquilizer–antidepressant

"...and she'd jump every time the phone rang."

"All right, I agree, she was obviously very anxious...you said she hadn't been sleeping..."

"She felt *tired enough* to sleep... not relaxed enough...food, too... she's too nervous to eat...says she *can't* relax...afraid there's something very wrong with her."

"...that's a good place to sta Did you find anything wron with her?"

Treatment with TRIAVIL—a balanced view.

Tablets TRIAVIL are available in four different combinations affording flexibility and individualized dosage adjustment. Close supervision of patients is essential until satisfactory remission has taken place. Since suicide is a possibility in any depressive illness, patients should not have easy access to large quantities of the drug. The drug may impair alertness and potentiate the response to alcohol. It should not be used during the acute recovery phase following myocardial infarction or given to patients who have received an MAOI within two weeks. TRIAVIL should be used with caution in glaucoma and in patients prone to urinary retention. It is contraindicated in CNS depression and in the presence of evidence of bone marrow depression.

MSD MERCK SHARP DOHME For a brief summary of prescribing information, please turn to the following page.

a thing... negative... nothing
anically wrong. Still has a
list of somatic complaints.
tried to reassure her... to let
talk... to help her sort things
She's been in to see me a
ber of times."

"...what about medication?"

"Just what I was coming to...
I've had her on tranquilizers.
And *that's* what puzzles me. I'm
not getting the response I hoped
for. She's no better... perhaps a
little worse. It's sad to see."

"...I think *'sad'* may be what
you're not seeing! You know,
this sounds like another case
where the *anxiety* is so clear and
pervasive we tend to overlook
the depressive part of the picture.
I'm not sure that we shouldn't
almost always think of anxiety
with depression... not anxiety
alone. Take another look at your
records... talk to her some more.
If you decide she's depressed,
I think you might want to
consider TRIAVIL.... It can help
relieve her entire symptom
complex... control the anxiety...
while at the same time treat
the depression."

TRIAVIL®

containing perphenazine and amitriptyline HCl

a tranquilizer–antidepressant

to help treat what you often find:
obvious moderate to severe anxiety
with a less obvious underlying depression

Available:
TRIAVIL® 2-25: Each tablet contains
2 mg. perphenazine and 25 mg. amitriptyline HCl

TRIAVIL® 2-10: Each tablet contains
2 mg. perphenazine and 10 mg. amitriptyline HCl

TRIAVIL® 4-25: Each tablet contains
4 mg. perphenazine and 25 mg. amitriptyline HCl

TRIAVIL® 4-10: Each tablet contains
4 mg. perphenazine and 10 mg. amitriptyline HCl

INITIAL THERAPY FOR MANY PATIENTS
TRIAVIL® 2-25 (or TRIAVIL® 4-25) t.i.d. or q.i.d.

FOR FLEXIBILITY IN ADJUSTING MAINTENANCE THERAPY
TRIAVIL® 2-10 (or TRIAVIL® 4-10)

CONTRAINDICATIONS: Central nervous system depression from drugs (barbiturates, alcohol, narcotics, analgesics, antihistamines); bone marrow depression; known hypersensitivity to phenothiazines or amitriptyline. Do not give concomitantly with MAOI drugs because hyperpyretic crises, severe convulsions, and deaths have occurred from such combinations. Allow minimum of 14 days between therapies, then initiate therapy with TRIAVIL cautiously, with gradual increase in dosage until optimum response is achieved. Not recommended for use during acute recovery phase following myocardial infarction.

WARNINGS: TRIAVIL should not be given with guanethidine or similarly acting compounds. Use cautiously in patients with history of urinary retention, angle-closure glaucoma, increased intraocular pressure, or convulsive disorders. Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressants, including amitriptyline HCl, particularly in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of conduction time. Myocardial infarction and stroke have been reported with tricyclic antidepressant drugs. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. Caution patients performing hazardous tasks, such as operating machinery or driving motor vehicles, that drug may impair mental and/or physical abilities. Not recommended in children or during pregnancy.

PRECAUTIONS: Suicide is a possibility in depressed patients and may remain until significant remission occurs. Such patients should not have access to large quantities of this drug.

Perphenazine: Should not be used indiscriminately. Use with caution in patients who have previously exhibited severe adverse reactions to other phenothiazines. Likelihood of untoward actions is greater with high doses. Closely supervise with any dosage. The antiemetic effect of perphenazine may obscure signs of toxicity due to overdosage of other drugs or make more difficult the diagnosis of disorders such as brain tumor or intestinal obstruction. A significant, not otherwise explained, rise in body temperature may suggest individual intolerance to perphenazine, in which case discontinue.

If hypotension develops, epinephrine should not be employed, as its action is blocked and partially reversed by perphenazine. Phenothiazines may potentiate the action of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) and atropine. In concurrent therapy with any of these, TRIAVIL should be given in reduced dosage. May also potentiate the action of heat and phosphorous insecticides.

Amitriptyline: In manic-depressive psychosis, depressed patients may experience a shift toward the manic phase if they are treated with an antidepressant. Patients with paranoid symptomatology may have an exaggeration of such symptoms. The tranquilizing effect of TRIAVIL seems to reduce the likelihood of this effect. When amitriptyline HCl is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with 1 g of ethchlorvynol and 75-150 mg of amitriptyline HCl.

Amitriptyline HCl may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

Concurrent administration of amitriptyline HCl and electroshock therapy may increase the hazards associated with such therapy. Such treatment should be limited to patients for whom it is essential. Discontinue several days before elective surgery if possible. Elevation and lowering of blood sugar levels have both been reported.

ADVERSE REACTIONS: Similar to those reported with either constituent alone.

Perphenazine: Side effects may be any of those reported with phenothiazine drugs: extrapyramidal symptoms (opisthotonus, oculogyric crisis, hyperreflexia, dystonia, akathisia, acute dyskinesia, ataxia, parkinsonism) can usually be controlled by the concomitant use of effective antiparkinsonian drugs and/or by reduction in dosage, but sometimes persist after discontinuation of the phenothiazine.

Tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy with phenothiazines and related agents has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Involuntary movements of the extremities sometimes occur. There is no known treatment for tardive dyskinesia; antiparkinsonism agents usually do not alleviate the symptoms. It is advised that all antipsychotic agents be discontinued if the above symptoms appear. If treatment is reinstituted, or dosage of the particular drug increased, or another drug substituted, the syndrome may be masked. It has been suggested that fine vermicular movements of the tongue may be an early sign of the syndrome, and that the full-blown syndrome may not develop if medication is stopped when lingual vermiculation appears.

Other side effects are skin disorders (photosensitivity, itching, erythema, urticaria, eczema, up to exfoliative dermatitis); other allergic reactions (asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions); peripheral edema; reversed epinephrine effect; hyperglycemia; endocrine disturbances (lactation, galactorrhea, gynecomastia, disturbances of menstrual cycle); altered cerebrospinal fluid proteins; paradoxical excitement; hypertension, hypotension, tachycardia, and ECG abnormalities (quinidine-like effect); reactivation of psychotic processes; catatonic-like states, autonomic reactions, such as dry mouth or salivation, headache, anorexia, nausea, vomiting, constipation, obstipation, urinary frequency or incontinence, blurred vision, nasal congestion, and a change in pulse rate; hypnotic effects; pigmentary retinopathy; corneal and lenticular pigmentation; occasional lassitude, muscle weakness, mild insomnia. Other adverse reactions reported with various phenothiazine compounds include blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia); liver damage (jaundice, biliary stasis); grand mal convulsions; cerebral edema; polyphagia; photophobia; skin pigmentation; and failure of ejaculation.

Amitriptyline: Note: Listing includes a few reactions not reported for this drug, but which have occurred with other pharmacologically similar tricyclic antidepressant drugs. *Cardiovascular:* Hypotension; hypertension; tachycardia; palpitation; myocardial infarction; arrhythmias; heart block; stroke. *CNS and Neuromuscular:* Confusional states; disturbed concentration; disorientation; delusions; hallucinations; excitement; anxiety; restlessness; insomnia; nightmares; numbness, tingling, and paresthesias of the extremities; peripheral neuropathy; incoordination; ataxia; tremors; seizures; alteration in EEG patterns; extrapyramidal symptoms; tinnitus. *Anticholinergic:* Dry mouth; blurred vision; disturbance of accommodation; constipation; paralytic ileus; urinary retention; dilation of urinary tract. *Allergic:* Skin rash; urticaria; photosensitization; edema of face and tongue. *Hematologic:* Bone marrow depression including agranulocytosis; leukopenia; eosinophilia; purpura; thrombocytopenia. *Gastrointestinal:* Nausea; epigastric distress; vomiting; anorexia; stomatitis; peculiar taste; diarrhea; parotid swelling; black tongue. *Endocrine:* Testicular swelling and gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido; elevated or lowered blood sugar levels. *Other:* Dizziness, weakness; fatigue; headache; weight gain or loss; increased perspiration; urinary frequency; mydriasis; drowsiness; jaundice; alopecia. *Withdrawal Symptoms:* Abrupt cessation after prolonged administration may produce nausea, headache, and malaise. These are not indicative of addiction.

OVERDOSAGE: Treatment is symptomatic and supportive. However, the intravenous administration of 1-3 mg of physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. On this basis, in severe overdosage with perphenazine-amitriptyline combinations, symptomatic treatment of central anticholinergic effects with physostigmine salicylate should be considered.

For more detailed information, consult your MSD Representative or see full Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486.

MSD
MERCK SHARP DOHME

Our prescription for your practice: Take MediManager and get plenty of sleep.

Security Pacific Bank is glad to introduce MediManager: A comprehensive financial management package for the physician and dentist.

MediManager is the most complete professional service package ever offered to physicians and dentists. It's designed to be of help in (1) patient billing and collection, (2) patient credit, (3) equipment financing, (4) acquisition of facilities, and (5) estate management.

MediManager features a computerized patient billing service with insurance form preparation capabilities. It offers remittance banking and payroll help, as well as a unique patient credit plan that gives you prompt payment for your services. MediManager provides commercial and real estate loans, equipment loans and leasing, auto leasing and locational assistance. Finally, it can help you with trusts, pension plans and profit-sharing programs.

Ask your branch manager about MediManager: Something special from Security Pacific Bank.

SECURITY PACIFIC BANK
SOMETHING SPECIAL

© 1973 SECURITY PACIFIC NATIONAL BANK MEMBER FDIC

new

DARVOCET-N®

50 mg. propoxyphene napsylate
and 325 mg. acetaminophen

Lilly TABLETS

Additional information available to the profession on request.
Eli Lilly and Company, Indianapolis, Indiana 46206

300104

THE WESTERN
Journal of Medicine

Refer to: Blau L, Kent L: Conservative and surgical aspects of disc lesion management—Follow-up review of 244 cases. West J Med 120:353-357, May 1974

Conservative and Surgical Aspects of Disc Lesion Management

Follow-Up Review of 244 Cases

LESLIE BLAU, MD, *and* LEON KENT, MD, *Los Angeles*

A follow-up study of 244 patients who were admitted to hospital with the diagnosis of discogenic disease between 1963 and 1970 was conducted to determine more precisely when conservative care should stop and a myelogram study followed by surgical decompression should be considered.

The number of patients who had electromyography was separately tabulated and totaled (154). Of these, 87 (56.5 percent) had normal and 67 (43.5 percent) abnormal findings. It is significant that 29 of the total had positive myelograms and operation, yet 16 (59 percent) of the 29 had normal electromyograms. This raises a question about how much confidence to place in negative electromyographic findings when deciding for or against surgical operation. However, negative electromyograms are very helpful in reassuring patients who are emotional and resistant to resuming useful activities.

A STUDY WAS UNDERTAKEN to evaluate the effectiveness of conservative treatment of patients with discogenic disease and the correctness of decisions for surgical decompression, to determine the value of electromyography in root compression syndromes, and to appraise the patients' own opinion of the result of their specific treatment. Follow-up questionnaires to determine the effectiveness and duration of benefits of conservative as compared with surgical treatment were submitted and the answers tabulated.

From the Department of Physical Medicine, Southern California Permanente Medical Group, Panorama City, and the University of Southern California School of Medicine, Los Angeles (Dr. Blau); and the Department of Neurological Surgery, Southern California Permanente Medical Group, Los Angeles (Dr. Kent).

Submitted September 12, 1973.

Reprint requests to: L. Blau, MD, 3720 Scadlock Lane, Sherman Oaks, CA 91403.

Materials

The study encompassed 500 patients who had been admitted to hospital with disc lesions in a seven-year period (1963-1970). Seven patients who had pre-existing laminectomy with fusion operation for instability were omitted. These 500 patients had 691 hospital admissions, for disease of the lumbar disc in 612 cases, the cervical disc in 78 and the thoracic disc in one. One hundred

TABLE 1.—*Follow-up of Patients Who Had Negative Myologram*

Patient	
1.	No further low back difficulty. Returned to full activities.
2.	A highly hysterical patient. Was dismissed by the medical group for abuse of privileges.
3.	Many outpatient visits. Went to chiropractor and psychiatrist. Resumed full activities.
4.	At time of discharge, 50 percent less pain. Never returned for follow-up and our questionnaire was returned undelivered.
5.	Was admitted by neurology service for diagnostic work-up; brachial pleus neuralgia. Recovered from all neurological abnormalities.
6.	Many outpatient visits after discharge. Hysterical patient. Returned to part-time work.
7.	Returned to work one month after discharge.
8.	Was lost to follow-up.
9.	Outpatient visit one month after discharge—"better"; up and about full time.
10.	Admission was by neurosurgeon for myelogram, which showed no abnormality. Lost to follow-up.

patients had two admissions and 30 patients had three or four.

Of the patients studied, 257 were men (50.6 percent). The average age was 39.3 years. The oldest patient was 84 and the youngest 17. The oldest one operated on was 70, and the youngest 20. The average hospital stay was 9.44 days, against 13.7 days reported by Hakelius.[1]

All patients of this study had discogenic disease with radicular pain. The regimen of treatment was as follows: All were confined to bed except for toilet privileges. All were treated with bedside pelvic traction of 20 to 30 pounds in the semi-Fowler position with knees and hips flexed to the extent of comfort, and cervical traction of 7 to 10 pounds with weights suspended from an overhead bar pulling the head in slight flexion. Heat applications by moist pack, followed by flexion exercises, were used only if they did not aggravate the pain. Many patients with acute disc herniation did not tolerate such measures, and in such cases heat could be applied to the low back with the patient in the side-lying position to avoid hyperextension. When the lesion was in the cervical spine, the patient was fitted with a simple felt collar that was stiffened at the back by taping tongue depressors of suitable lengths to the felt. Covered with a stockinette and fastened firmly in place, the collar held the neck to very limited mobility and in slight flexion. Collars were used whenever traction had to be interrupted for relief of discomfort. Every patient received a muscle relaxant or a tranquilizer deemed most suitable. Analgesics were given by mouth or parenterally as needed.

After seven to ten days, if incapacity continued, symptoms persisted and signs of objective root compression remained, electromyography was done (provided symptoms had been present for at least three weeks) and neurosurgical consultation was requested as to the need for myelography and possible surgical decompression. When pain decreased to an estimated 50 to 60 percent of its highest intensity, the patient was discharged to outpatient care and was either fitted with a lumbo-sacral corset or instructed to continue pelvic or cervical traction at home. Apparatus for pelvic traction was made available for rent. These measures decreased the length of stay in hospital.

One hundred sixteen patients (23 percent) had laminectomy and discectomy—at the lumbar level in 108 cases, cervical in seven and thoracic in one. All patients were treated conservatively at first for one or two weeks, unless there was a neurogenic bladder condition or a progression of muscle weakness. Many of these patients had had complete bedrest at home for a week or two, some with pelvic traction, before admission.

In all cases in which surgical decompression was carried out, the myelogram was positive. Information on ten patients who had negative myelograms is given in Table 1. The surgical decompression in almost all the cases was carried out by the same neurosurgeon using the same operation technique. Surgical decompression consisted of simple laminotomy at the site of root compression, with careful removal of all disc fragments which were extradural, as well as all the disc material from the intervertebral interspace. Further root decompression was carried out by unroofing the nerve root canal. Very early ambulation, usually on the first or second postoperative day, was encouraged. The great majority of the patients were discharged between the sixth and eighth postoperative day. Fusion was performed only in the rare case in which there was concomitant spondylolisthesis of the kind associated with congenital defect.

Indication for operation remains the most difficult aspect of discogenic root compression. Since prognosis is uncertain and neurological abnormalities such as muscle weakness may persist after operation, delay is justified because the neurologi-

cal deficit frequently resolves itself during conservative therapy. The two following case reports will illustrate these points.

CASE 1. A tool and die maker 56 years of age was first admitted 21 August 1966 with diagnosis of degenerative disc disease of the cervical spine. He complained of posterior cervical muscle stiffness and pain, with radiation into the right shoulder and elbow, as well as numbness of the index finger and thumb. Cervical spinal movements were limited, posterior cervical muscles were increased in tone, and posterior cervical and suboccipital tenderness was noted. The right deltoid and bicep muscles graded 50 to 60 percent. An x-ray study of the cervical spine done a month before admission showed degenerative changes from the fourth to the seventh vertebrae. The patient was discharged from the hospital after three days, pain having diminished. Neurosurgical and physical medicine consultants recommended continued conservative care. Subsequently the patient recovered from all neurological deficit of the right upper extremity. He was readmitted 3 October 1966 with diagnosis of root and cord pressure at the level of the fifth to sixth cervical (C5 and C6) vertebrae on the left side. He complained of "paralysis" of the left shoulder. On examination slight wasting of the shoulder girdle muscles was noted. The left biceps reflex was considerably depressed and there was hypesthesia of the C5 and C6 dermatomes. The left deltoid muscle graded only 30 to 40 percent. A cervical myelogram done at this time was reported by the radiologist as follows: "The contrast material was arrested at C5-C6 level and was beginning to break up at C6-C7; some trickled past this level. When the patient was upright, the contrast material was arrested at the C4-C5 level but trickled further when he was shaking his head." A partial block at C4-C5 to C6-C7 was considered to be due to spondylosis and thickened ligaments.

Operation was recommended but the patient decided against it and was discharged with instruction to continue cervical traction, intermittent wearing of a collar, use of heat applications, and neck flexion exercises. Muscle relaxants were also prescribed. He gradually recovered completely. Two years after his discharge from hospital there was no evidence of any neurological deficit in the upper extremities. Shoulder muscle strength was normal on both sides and the patient was working full-time at his job. On examination at the end of five years, there was no regression or recurrence of symptoms.

CASE 2. A 57-year-old housewife was admitted to hospital 19 July 1964 with a diagnosis of lumbar discogenic disease. Complaints were low back pain with radiation into the left lower extremity, and difficulty in micturition. Laseque's sign was present in the left hip. There was weakness of the left peronous longus and toe extensor muscles, and hypesthesia of the dorso-lateral aspect of the foot. The left ankle reflex was depressed and the patient was unable to stand on the left heel. She had great difficulty in initiating micturition and had to have an indwelling catheter for proper drainage due to neurogenic bladder dysfunction.

An x-ray film of the lumbo-sacral spine showed no abnormality. An extradural defect at the level of the fifth lumbar to first sacral vertebrae consistent with herniated nucleus pulposus on the left side was shown on a myelogram. Laminectomy the following day confirmed the myelographic findings. Surgical decompression relieved the urinary symptoms, but the patient continued to have weakness of the peroneus longus and toe extensors. This weakness required the wearing of a drop-foot brace even six years after operation.

Case 1 illustrates that conservative care and time may resolve severe effects of root compression and that emergency operation may not be necessary. Case 2 indicates that even prompt surgical decompression may not reverse symptoms such as weakness. As a result of this uncertainty in the prognosis of the root syndrome, one must determine that the underlying disease is not an expanding lesion, such as a tumor. That was the reason for myelogram in the two cases here reported. A second consideration is intractable pain that is not relieved by conservative means within a reasonable time. This has been a deciding factor for operation, following a positive myelogram, in many of our cases. Neurogenic bladder dysfunction may also be an indication for visualization by myelogram and then surgical decompression if it is determined that the dysfunction is not simply based on hypotonia caused by drugs and inability to void due to pain.

Electromyography

Electromyographic examinations were done in 154 (38 percent) of the patients to help in establishing the final diagnosis. In 67 cases (44 percent) the result was positive. The test was considered positive when one or more muscles in the

TABLE 2.—*Results of Conservative Treatment as Determined by Answers to Questionnaire*

Rating	*Number*	*Percentage*
Excellent	54	29.3
Good	66	35.8
Fair	43	23.3
Poor	18	9.8
Expired	3	1.8
TOTAL	184	100.0

TABLE 3.—*Rating of Results in Surgical Patients Based on Replies to Questionnaire*

Rating	*Number*	*Percentage*
Excellent	30	50
Good	15	25
Fair	11	18
Poor	4	7
TOTAL	60	100

TABLE 4.—*Self-Appraisal of Results, Surgical Patients*

Rating	*Number*	*Percentage*
Excellent	35	58.3
Good	18	30.0
Fair	4	6.7
Poor	3	5.0
TOTAL	60	100.0

limb (anterior primari rami) or erector spinae (posterior primari rami) showed fibrillation potentials. It is recognized that theoretically one should find such involvement in all muscles of the myotome innervated by the anterior and posterior primari rami of that root, as described by Marinacci.[2] However, in 25 years' experience with clinical electromyography, I have rarely observed degeneration of the entire myotome. In this regard it should be noted that DeCoul and Lie[3] said that electromyographic studies have important limitations in that they depend on the patient's tolerance to pain and on the investigator's time and patience. To determine root involvement the following muscles in the lower extremity are routinely sampled: anterior tibial, peroneus longus, both heads of the gastrocnemius, gluteus medius and maximus, and the erector spinae from the second lumbar to the second sacral level. In the cervical segment, samplings are made of the deltoid, biceps, triceps, extensor carpi radialis, opponens pollicis and abductor digiti quinti as well as the erector spinae from the fifth cervical to the first thoracic level. Examination involves one or two punctures of the muscle and moving the needle electrode in a full circle following the steps recently described by Johnson et al.[4] The muscle is investigated while at rest for fibrillation, positive sharp waves, fasciculations and myotonic outbursts, and then again during mild and finally during maximal contractions.

Surgical decompression was done in 29 of the 154 patients who had electromyography. Of the 29 patients who had operation and proven root pressure, 16 (59 percent) had had negative electromyographic findings, though in all cases myelograms had shown deficits or impaired root filling. All had clinical evidence of neurological deficit and intractable radicular pain.

The total number of this study is not large but the observations cast doubt on the reliability of electromyography as a guide in the management of root compression syndromes. Such uncertainty may explain widely divergent opinions expressed in the literature, ranging from DePalma's view that it is of no significant value[5] to Brady's opinion that it is of equal value or superior in accuracy to examination by myelogram.[6] Electromyography serves a useful purpose when the results are positive, as it shows involvement when clinical diagnosis is equivocal and incapacity might be attributed to pain. This permits more definitive treatment and helps in deciding whether to have a myelographic study and possibly surgical operation. On the other hand a negative electromyogram may be helpful in coping with a patient who expresses fear that resuming useful activities or his usual vocational pursuits will aggravate his pain. With confirmatory evidence that there is no surgical lesion, he can more easily be persuaded that the best treatment for him is to carry on normal activities and return for follow-up examination.

Results

Questionnaires, with addressed and stamped return envelopes, were mailed to all 500 patients, 244 of whom responded (48.8 percent). Returns were rated according to the number of favorable answers to questions such as: "Did you have further difficulties?", "Did you return to full activities?", "Did you receive further care from other sources?" If all three answers were favorable, the rating was *excellent;* if two, *good;* if one, *fair;* and if none, *poor.* In the surgical cases the patient's subjective appraisal was also requested. (See Tables 2, 3, and 4.)

Of the non-surgical cases, 120 (49 percent of 244 replies) were rated excellent or good. Of the

60 surgical patients who replied, 53 (88 percent) indicated excellent or good results according to their own appraisal. When these were rated on the same basis as that used in rating the non-surgical cases, 45 patients (75 percent) showed excellent or good results. Comparable results have been reported by other investigators.[7]

In their questionnaire answers, 181 patients (74.2 percent) indicated return to full activities. The remaining 25.8 percent either returned to partial, lighter work or did not answer this question.

The average time between operation and return to work in the 116 surgical cases was 84.3 days when the operation was on the lumbar spine and 92 days when on the cervical spine. The one patient who had thoracic spine laminectomy returned to work in 45 days.

Of 108 patients who had lumbar surgical decompression, ten had recurrence of pain. Seven of these ten then were treated conservatively, three by reoperation. One of the seven patients who had operation for cervical disc disease had recurrence of pain and was treated conservatively. In this case, in which the patient had been operated on for symptoms of cord pressure, parkinsonism eventually developed on the basis of cerebral arteriosclerosis. The patient became totally incapacitated but was benefited by levadopa.

Discussion

The objective evaluation of treatment comparing conservative with surgical treatment of patients with root compression syndrome caused by discogenic disease indicates no substantial difference: 65 percent of the non-surgically treated had excellent and good ratings, as compared with 75 percent of patients surgically treated.

The surgically treated patients' own appraisal of the results showed 88.3 percent thought they were excellent or good. It should be pointed out also that twice as high a proportion of surgically treated as conservatively treated patients considered their results excellent. If the 116 cases which came to surgical therapy are looked upon as a reflection of failure of conservative treatment, then the difference in the proportion of favorable results—65 percent in the conservative and 75 percent in the surgical series—becomes 49 percent for conservative against 75 percent for surgical on our rating, and 49 percent against 88.3 percent by the patients' self-appraisal. This difference is statistically significant.

REFERENCES

1. Hakelius A: Prognosis in sciatica. Acta Orthop Scand [Suppl] 129:5-76, 1970

2. Marinacci AA: Clinical Electromyography. San Lucas Press, 1955, p 97

3. Lie TA, AAW Op DeCoul: A comparative electromyographic study before and after operations for protruded lumbar disc. Electromyography, 1970, pp 193-199

4. Johnson EW, Melvin JL: Value of electromyography in lumbar radiculopathy. Arch Phys Med Rehabil 52:239-243, 1971

5. DePalma AF, Rothman RH: The Intervertebral Disc. Philadelphia, W. B. Saunders Co., 1970, p 230

6. Brady LP, Parker LB, Vaughn J: An evaluation of the electromyogram in the diagnosis of the lumbar disc lesion. J Bone Joint Surg 51-A:539-547, 1969

7. Barr J, Kubik CS, Molloy M, et al: Evaluation of end results in treatment of ruptured lumbar intervertebral disks with protrusion of nucleus pulposus. Surg Gynec Obstet 125:250-256, 1967

Refer to: Mahler RJ: Diabetes mellitus—Distinguishing between patients receiving insulin and those requiring insulin therapy. West J Med 120:358-362, May 1974

Diabetes Mellitus

Distinguishing Between Patients Receiving Insulin and Those Requiring Insulin Therapy

RICHARD J. MAHLER, MD, *Palm Desert, California*

Fifteen patients with maturity onset type diabetes, all of whom had received insulin for periods of one to thirty-five years, were admitted to hospital and insulin treatment was discontinued. Within 24 to 48 hours each patient was given an intravenous tolbutamide test, following which all were given either diet therapy alone or diet therapy plus oral agents. If significant hyperglycemia or ketonemia resulted, insulin therapy was reinstituted.

Approximately 50 percent (8 of 15) of the patients showed improvement in fasting blood sugar levels following discontinuation of insulin. It was not possible to distinguish the insulin independent from the insulin dependent group using such criteria as age, sex, degree of overweight, insulin dosage, duration of diabetes or duration of insulin therapy. However, using the intravenous tolbutamide test it was possible to differentiate between the two groups. Those who did not require insulin responded to intravenous tolbutamide with a glucose decrease greater than 10 percent from the initial value. The insulin dependent group had either no glucose decrease or a rise in blood glucose following intravenous administration of tolbutamide.

ALMOST FROM THE MOMENT of the successful extraction and purification of insulin in 1922,[1] up to the advent of oral hypoglycemic therapy in 1956,[2] it was thought necessary to treat all hyperglycemia with exogenous insulin. Still today, large numbers of diabetic persons receive exogenous insulin injections daily although their need for insulin has not truly been established. Several recent articles have noted this fact[3-6] and attempts have been made to differentiate between the juvenile onset type of diabetic patient (typically lean, ketosis-prone and truly insulin dependent) and the maturity onset type of diabetic (generally overweight, ketosis-resistant and insulin independent).

Unfortunately this division of diabetic patients

From the Department of Metabolism and Endocrinology, City of Hope Medical Center, Duarte, California.

Submitted September 4, 1973.

Reprint requests to: R. J. Mahler, MD, Director, Department of Metabolism and Endocrinology, Eisenhower Medical Center, 39000 Bob Hope Drive, Palm Desert, CA 92260.

TABLE 1

Patient	Sex	Age	Height (inches)	Weight (pounds)	Percent Over Ideal Weight	Duration of Diabetes (years)	Insulin Therapy (years)	Last Insulin Dose (units)	Blood Glucose on Insulin (mg%)	Blood Glucose on Diet and Oral Agents (mg%)	Intravenous Tolbutamide Test Fasting 60 Min. (mg%)	(mg%)
1*	M	55	72	211½	33	35	35	120	198	80	224	193
2*	F	40	60	177¼	70	6	6	35	378	126	152	136
3*	M	73	70½	199	30	10	2	90	204	129	184	158
4*	F	66	63½	174	30	15	15	35	259	229	234	204
5*	F	63	62½	189	45	8	8	45	179	66	163	135
6*	M	58	69	169	10	15	2	60	110	112	164	151
7*	F	53	52	226	70	5	3	90	263	125	294	247
8*	F	53	64	157	10	2	1	70	223	134	149	129
9†	M	84	64¼	166½	20	6	5	76	334	..	225	246
10†	F	49	60½	146	20	8	8	36	281	..	244	260
11†	F	80	61	129¼	10	22	9	120	250	..	235	236
12†	M	51	69	158	0	1	1	24	194	..	215	213
13†	M	49	66	115	0	1	1	60	80	..	146	165
14†	F	55	63	116	0	5	5	22	260	..	237	303
15†	M	29	72	175½	4	16	16	60	209	..	327	320

*"Responders" †"Non-responders"

is artificial and all too often fails. One finds a considerable number of children with maturity onset type diabetes[7] and some arbitrarily termed maturity onset insulin independent diabetics may actually require insulin for the prevention of ketosis. Therefore, distinguishing those persons who are presently receiving insulin without actually requiring it, from those who require insulin and are receiving it, has been a difficult task. All previous efforts have entailed admitting the patient to hospital, withdrawing insulin and waiting for ketosis to develop.

The ultimate test of insulin independency is the effectiveness of the endogenous insulin response. Therefore, we suggest that a simple method of identifying insulin independency in diabetic patients is through a rapid test of pancreatic insulin reserve.[8]

Materials and Methods

Fifteen patients were selected for study. The age range was from 29 to 84 years and the duration of diabetes ranged from ten months to 35 years (Table 1). All patients were receiving insulin, with the length of therapy varying from ten months to 35 years (none had ever previously shown signs of ketoacidosis).

All patients were admitted to our metabolic unit, their last insulin injection having been given on the morning of admission to hospital. They were placed on a diet of approximately 20 calories per kg with 40 percent carbohydrate, 40 percent protein and 20 percent fat. The patients were given three meals daily, with afternoon and bedtime snacks. No food was given after 10:00 p.m. and on the following morning in the case of those who had been receiving intermediate acting insulin preparations, or two days later in those cases where long acting insulins had been used, an intravenous tolbutamide test* was carried out according to the following procedure. An infusion of normal saline solution was started, through an 18 gauge needle connected to a three-way stopcock. Three fasting blood specimens were collected at five-minute intervals, and immediately after the third sample was taken, 1.0 gram of sodium tolbutamide dissolved in 20 ml of diluent was injected. Blood specimens were collected every ten minutes during the next hour, the blood was allowed to clot and serum specimens were analyzed for glucose by autoanalyzer, using a ferricyanide method.[9] Thereafter all patients were observed on diet therapy alone.

If the fasting blood sugar exceeded 300 mg per 100 ml after five days of diet therapy alone, then oral agents were administered, either phenformin alone or phenformin in combination with clorpropamide. These oral agents were discontinued and insulin reinstituted if the blood sugar level remained above 300 mg per 100 ml, or if more than moderate acetonuria was observed or if the serum acetone became detectable in the undiluted specimen at any time. If the blood glucose level of patients on diet therapy alone or diet therapy plus oral agents fell below 200 mg per 100 ml or

*Orinase Diagnostic®—The Upjohn Company.

became lower than the initial glucose value while they were receiving insulin, then they were deemed "responders."

The Student test was used for testing the significance of difference between two means.[10]

Results

Of the 15 patients studied, eight were found to be improved following discontinuation of insulin therapy. The average age of those who responded to diet therapy alone or diet therapy plus oral agents (termed "responders") was almost identical to the average age of those patients (termed "non-responders") who eventually required reinstitution of insulin (58 years and 57 years respectively).

There were five female and three male responders as compared with three female and four male non-responders.

The average duration of diabetes in the responders was twelve years with a range of two to thirty-five years. This did not differ greatly from the average duration of nine years and the range of one to twenty-two years for the non-responders.

Similarly the duration of insulin therapy in the responders averaged nine years (ranging from one to 35 years) as compared with a six-year average duration of therapy (ranging from one to sixteen years) in the non-responders.

The daily insulin dosage for those patients who responded had averaged 68 units a day which compared closely with the average daily insulin requirement of 57 units a day in the non-responder group. Considerable overlap of insulin dosage occurred in both groups (Table 1).

On the average, those patients that responded were more overweight than the non-responders (33 percent above ideal body weight and 8 percent above ideal body weight respectively*). However, two patients weighing less than 10 percent above ideal body weight responded to diet alone and two patients weighing more than 20 percent above ideal body weight failed to respond to insulin withdrawal. Thus the degree of overweight is not an invariable determinant of responsiveness.

The mean initial fasting blood glucose value of the responders did not differ greatly from that of the non-responders (227±32 vs 230±30 mg per 100 ml) (mean±S.E.M.). After discontinuation of insulin therapy, there was no decrease or further rise in fasting blood glucose in the non-responders. However, there was a significant decrease in fasting glucose values in those patients who did respond to insulin withdrawal (125±20 mg per 100 ml after vs 227±32 mg per 100 ml before) (mean±S.E.M.) ($p<.01$).

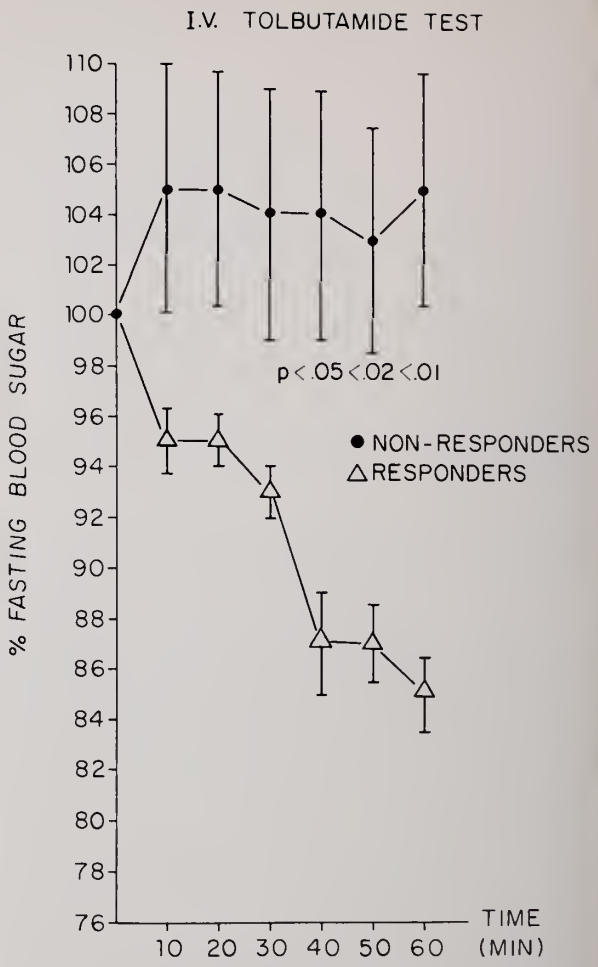


Chart 1.—Intravenous tolbutamide test. Non-responders vs Responders. Figures represent mean ± S.E.M. For details see text.

Finally, the intravenous tolbutamide test clearly distinguished the responders from the non-responders in that the responders had a glucose fall greater than 10 percent of the fasting value 60 minutes following tolbutamide injection whereas the non-responders demonstrated no glucose change or an increase in blood glucose level after tolbutamide injection. There were no exceptions (Chart 1).

The eight responders were asked to return for reevaluation six months following initial tolbutamide testing. One patient died of acute myocardial infarction three months after discontinuation of insulin and initiation of diet plus orinase therapy.

*Based on tables of ideal body weight, Metropolitan Life Insurance Co., New York.

All of the remaining seven responders were continuing to do well without exogenous insulin—four in control with diet alone, one receiving diet plus chlorpropamide (Diabinese®) and DBI®,* one receiving diet plus tolazamide (Tolinase®) and DBI, and one receiving diet plus tolbutamide (Orinase®). Repeat intravenous tolbutamide tests were performed on six of the seven responders. Sixty minutes following intravenous tolbutamide injection the glucose value fell to 87±4 percent (mean±S.E.M.) of the pre-injection sugar level. This response was in accord with the results obtained during tolbutamide testing six months previously (Chart 1) and suggests that pancreatic responsiveness remained unaltered following six months of insulin withdrawal and out-patient observation in these patients.

Discussion

There is an apt analogy of the depancreatized animal to that of the juvenile onset diabetic person, since both are characterized by an "absolute deficiency of insulin."[11] Without treatment, both the human and the animal model promptly develop hyperglycemia and ketosis and then die. Insulin therapy will prevent ketosis, improve the rate of glucose utilization and maintain the life of the individual. In this clinical setting, administration of insulin is absolutely essential.

A vastly different clinical picture characterizes persons with maturity onset type diabetes. Frequently overweight, they show signs of hyperglycemia without ketosis. Although their insulin response to glucose challenge may be delayed,[12] the level of insulin in the serum is at least normal and is sometimes greater than normal.[13,14] Moreover, the amount of injected insulin which is capable of producing a significant lowering of the blood sugar exceeds by far the amount required to produce a comparable effect in patients with juvenile onset type diabetes.[15] Consequently the maturity onset type diabetic is said to be "insulin resistant."

The insulin resistance that characterizes maturity onset type diabetes is unique. Rather than binding insulin and thereby interfering with all of its metabolic effects as would typify insulin resistance due to excessive antibody production,[16] the insulin resistance of maturity onset type diabetes appears to exert tissue specificity. Although liver and muscle tissues are almost certainly affected,[17,18] there appears to be no impairment in the incorporation of glucose into adipose tissues. In fact, this pathway is likely to be favored since obesity exists in fully 80 percent of maturity onset type diabetics.[19] Somehow linked, through mechanisms unclear at present, is the association between obesity and insulin resistance. The greater the obesity, the greater the insulin resistance.[20] Based on recent information, it is not likely that insulin resistance is caused by obesity in itself. Rather, pancreatic hypersecretion existing during the obese state,[21,22] appears to alter tissue insulin receptors,[23] resulting in insulin resistance.

Since hyperinsulinism begets obesity and obesity begets insulin resistance, the least desirable manner of treating maturity onset type diabetes compounded by overweight and insulin resistance would be the further administration of insulin. Rather, caloric restriction and concomitant weight reduction, through presently undefined mechanisms, will cause a lowering of elevated plasma insulin level and amelioration of insulin resistance. If this delicate balance is tipped in favor of insulin, improvement in glucose tolerance will result.

Unfortunately, this simplified approach is not applicable to all presumably maturity onset type diabetic subjects. Some of these persons, despite being overweight and insulin resistant, appear to suffer from absolute insulin lack. It should be pointed out that this group is clearly distinguishable from the obviously insulinopenic and explosively ketotic juvenile onset type diabetic. Rather, their insulin dependency is subtle. If they are left untreated, hyperglycemia will increase insidiously and ketosis will delay but eventually become evident.[4]

It is difficult but essential to differentiate these seemingly maturity onset type but truly insulin dependent diabetics from those who truly have maturity onset type diabetes. Criteria such as age, sex, duration of diabetes, degree of overweight, and amounts of injected insulin necessary to lower the blood sugar level have proven to be of no use.[3-6] Lev-Ran has suggested that the duration of insulin therapy might identify those who are truly insulin dependent.[4] However, we now report one patient (Case 1 in Table 1) and have since identified a second patient who each have taken insulin for 35 years and neither now requires it.

The intravenous injection of sodium tolbutamide has been proposed as a means of diagnosing the presence of diabetes mellitus, based on the

*DBI®, a preparation of phenformin hydrochloride.

principle that the magnitude of hypoglycemia so produced is directly dependent upon the effective endogenous insulin response.[8] As defined by Unger and Madison, a glucose fall of less than 10 percent from the initial value after 10 minutes and a fall of less than 17 percent after 30 minutes indicates the presence of diabetes mellitus. Moreover the rate of descent of the blood sugar level following tolbutamide injection was seen to be delayed in the diabetic so that the sugar level was still declining after 60 minutes in the diabetic group. However, the glucose values had reached their nadir and were starting to return toward the initial value in the normal control subjects 60 minutes following tolbutamide injection.

We believe that this test can be used to further divide the diabetic population into those who are devoid of pancreatic responsiveness and those who have a deficient but still discernible endogenous pancreatic reserve. We further consider that use of the intravenous tolbutamide test, as described within this report, fulfills the need to readily identify the 30 percent to 60 percent of maturity onset type diabetic persons receiving insulin who do not actually require it.[3-6]

REFERENCES

1. Banting FG, Best CH: The internal secretion of the pancreas. J Lab Clin Med V11:251-266, 1922

2. Loubatieres A: Use of certain sulfonamides in the treatment of experimentally induced diabetes mellitus: Personal research (1942-1946). Presse Med 63:1701-1703, 1955

3. Fineberg SK: Combinations of oral hypoglycemic drugs in obesé, insulin resistant diabetics. Geriatrics 23:137, 1968

4. Lev-Ran A: Treatment with chlorpropamide-phenformin combination in adult, obese ketosis-resistant diabetics. Israel J Med Sci 7:727, 1971

5. Knick B, Wendt O, Konder ML, et al: Non-indicated insulin treatment. Acta Diabet Lat 7:421, 1970

6. Singer DL, Stewart RC, Hurwitz D: Chlorpropamide in patients on high insulin dosage. N Engl J Med 265:823-826, 1961

7. Rosenbloom AL, Drash A, Guthrie R: Chemical diabetes mellitus in childhood. Diabetes 21:45-49, 1972

8. Unger RH, Madison LL: A new diagnostic procedure for mild diabetes mellitus. Evaluation of an intravenous tolbutamide response test. Diabetes 7:455-461, 1958

9. Hoffman WS: A rapid photoelectric method for the determination of glucose in blood and urine. J Biol Chem 120:51-55, 1937

10. Winer BJ: Statistical Principles in Experimental Design. New York, McGraw Hill Book Co., 1962

11. Parker ML, Pildes RS, Chao KL, et al: Juvenile diabetes mellitus, a deficiency in insulin. Diabetes 17:27-32, 1968

12. Cerasi E, Luft R, Efendic S: Decreased sensitivity of the pancreatic beta cells to glucose in prediabetic and diabetic subjects. Diabetes 21:224-234, 1972

13. Yallow RS, Berson SA: Immunoassay of endogenous plasma insulin in man. J Clin Invest 39:1157, 1960

14. Karam JM, Grodsky GM, Forsham PM: Excessive insulin response to glucose in obese subjects as measured by immunochemical assay. Diabetes 12:197-204, 1963

15. Himsworth HP: Diabetes mellitus. Lancet 1:127-130, 1936

16. Anderson JW, Kilbourn KG, Robinson J, et al: Diabetic acidosis in rats treated with anti-insulin serum. Clin Sci 24:417-430, 1963

17. Felig P, Wahren J: Influence of endogenous insulin secretion on splanchnic glucose and amino acid metabolism in man. J Clin Invest 50:1702-1711, 1971

18. Reaven GM, Silvers A, Farquhar JW: Study of the relationship between plasma insulin concentration and efficiency of glucose uptake in normal and mildly diabetic subjects. Diabetes 19:571, 1970

19. Marks HH, Krall LP, White P: Epidemiology and detection of diabetes, *In* Joslin's Diabetes Mellitus. Philadelphia, Lea & Febiger, 1971, pp 10-34

20. Sims EAH, Kelleher PE, Horton ES, et al: Experimental obesity in man, *In* Vague J (Ed): Physiopath. of Adipose Tissue. 1969, Exerpta Medica, pp 78-92

21. Mahler RJ, Szabo O: Amelioration of insulin resistance in obese mice. Am J Physiol 221:980-983, 1971

22. Mahler RJ: Advances in metabolic disorders. (In press)

23. Kahn CR, Soll A, Neville DM Jr, et al: Severe deficiency in insulin receptors: A common denominator in the insulin resistance of obesity. Clin Res 21:628, 1973

Refer to: Palmer JM: Differential antibiotic excretion in unilateral structural pyelonephritis. West J Med 120:363-368, May 1974

Differential Antibiotic Excretion in Unilateral Structural Pyelonephritis

JOHN M. PALMER, MD, *Davis, California*

Differential antibiotic excretion studies in eight patients wlth unilateral structural pyelonephritis showed that in all instances there was impairment in antibiotic excretion on the affected side compared with the normal kidney. Both peak and mean urinary concentrations were decreased on the structurally abnormal side. The degree of defect in antibiotic concentration was proportional to the amount of unilateral medullary damage, as measured by differential renal function studies. While the antibiotic concentrations achieved had an inconsistent relationship to cure in three patients with proven unilateral infections, the striking decreases in urinary antibiotic levels may argue against oral penicillin-G treatment of unilateral pyelonephritis in which there is renal parenchymal damage.

THE EFFECTIVENESS of penicillin-G against most Gram-negative organisms *in vitro* is well recognized and its use in treating urinary tract infection has been advocated. This treatment is usually recommended for infra-nephric infections, however, and great reliance is placed on the increased urinary concentration of antibiotic to promote its effectiveness.[1-3] Oral penicillin-G at a dose of 3.2 million units per day when administered without food has been shown to produce mean urinary concentrations of antibiotic in excess of 300 μg per ml in normal volunteers.[4] These data have recently been substantiated by Hulbert.[5] Such concentrations exceed the minimum inhibitory concentration (MIC) for most urinary pathogens. Stamey[6] has advocated therapy with penicillin-G for susceptible organisms, and good results in the treatment of bacteriuria emanating from the upper tract are documented by ureteric catheterization.

In the presence of infected urinary calculus disease, in urologic obstruction with infection or in renal failure, therapeutic urinary levels either may not be achieved or, if achieved, may be ineffective in clearing the infection. In these instances intensive antibiotic therapy is crucial, usually with associated surgical treatment except in chronic renal disease. Similar frustration of therapy occurs in *unilateral* structural pyelonephritis where severe parenchymal damage has occurred. We have noted in such cases that despite appropriate treat-

From the Department of Urology, Division of Surgical Sciences, University of California, Davis, School of Medicine.

Submitted, revised, September 10, 1973.

Reprint requests to: J. M. Palmer, MD, Department of Urology, University of California, Davis, School of Medicine, Davis, CA 95616.

ment based on sensitivity testing, it is the exceptional patient who is cured of infection with urinary level antibiotic therapy. Failures in such patients could be attributed to micro-abscesses interfering with antibiotic perfusion of medullary tissue within the renal parenchyma, or to the presence of micro-calculi serving as reservoirs of infection. Either explanation is possible since the identical organism recurs after appropriate therapy in most instances, usually with unchanged antibiotic sensitivities. A third possibility is the failure of impaired tubular concentrating mechanisms on the involved side to achieve sufficient medullary antibiotic levels to clear the infection. In order to test this third hypothesis, eight patients with unilateral structural pyelonephritis were studied by ureteric catheterization. Standard renal function tests were made and differential antibiotic concentrations were determined.

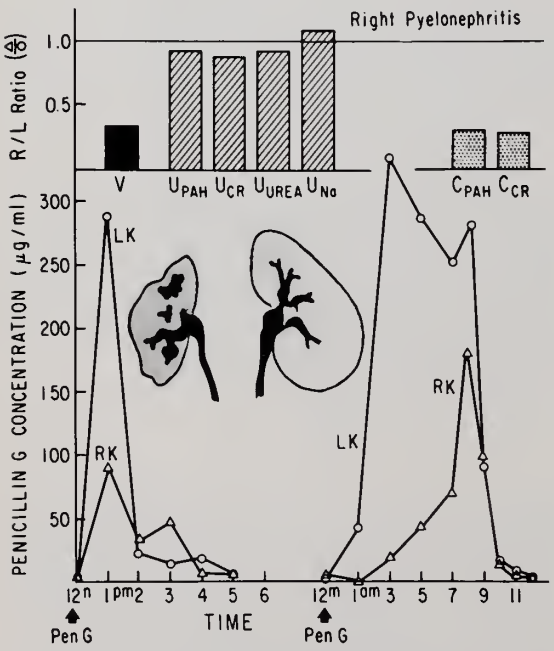


Chart 1.—Documented Right Pyelonephritis. Urine volume, U_{PAH}, U_{Cr} and U_{Urea} are all decreased with an increase in U_{Na} on the infected side compared with the normal kidney. Clearance ratios show marked functional impairment on the right side. Peak urinary penicillin concentrations are substantially greater in the non-infected left kidney. Mean urinary penicillin concentration on the right was 31 μg per ml and was 57 μg per ml on the left (Table 1).

The *P. mirabilis* isolated from the right kidney was found to be resistant to penicillin-G (MIC = >512 μg per ml). Here the MIC far exceeded the concentration of 31 μg per ml in the right renal urine. The patient remains asymptomatic when given maintenance dosages of ampicillin although *P. mirabilis* can be recovered from urine when therapy is interrupted.

Methods

In eight women patients with a history of recurrent urinary tract infections, the results of excretory urography were consistent with unilateral atrophic pyelonephritis. In all affected kidneys a decrease in renal size was apparent and there was cortical scarring adjacent to blunted calyces. The contralateral kidney showed no consistent calyceal changes and in most instances was enlarged. Additional urologic work-up showed vesicoureteral reflux in two patients. One patient was being evaluated for hypertension and inactive unilateral renal tuberculosis. In five of the eight patients

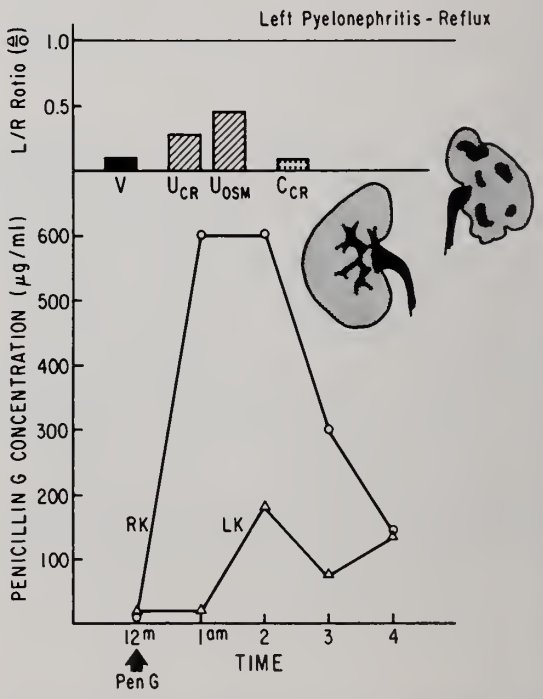


Chart 2.—Documented Left Pyelonephritis. Urine volume, U_{Cr} and U_{Osm} (osmolarity) ratios are severely reduced in this patient with proven left renal infection. The damaged left kidney constitutes less than 10 percent of the total renal function. Urinary penicillin concentration peaks at 600 μg per ml on the normal side, over three times the level achieved on the infected side. The comparative delay in peak concentration probably relates to dead-space error from low urine volume on left. The mean left urinary concentration was 87 μg per ml, less than 30 percent achieved on the right side (Table 1).

Left vesicoureteral reflux was present. The *E. coli* recovered from the left kidney was sensitive to penicillin-G at 38 μg per ml. Mean urinary concentrations from this kidney exceeded this at 87 μg per ml. Despite this, repeated courses of penicillin-G failed to clear this *E. coli* which recurred within several days of cessation of therapy. Although serotyping was not done, repeat testing showed identical sensitivity. Long term therapy with cephaloglycin was equally ineffective and nephrectomy was ultimately necessary to control morbidity from infection.

differential ureteric catheterization studies localized the infection unilaterally to the abnormal kidney. In no instance was infection found on the contralateral side. Two patients were not infected at the time of antibiotic excretion studies and one had infection confined to the bladder.

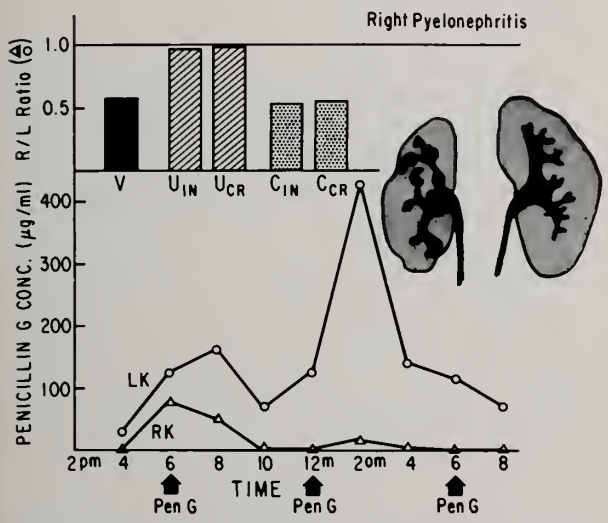


Chart 3.—Documented Right Pyelonephritis. Minimal differences in U_{In} and U_{Cr} are present in this patient during hydration, despite depressed clearance values on the infected right side. During the antibiotic excretion study consistently lower concentrations were found on the right side, although the mean concentration ratio of 0.11 (Table 1) is probably skewed by the peak concentration of 400 μg per ml on the normal side after the second dose.

The *E. coli* isolated from the right kidney was sensitive to penicillin-G at 49 μg per ml. The mean concentration of antibiotic in the urine was only 16 μg per ml during the study, but the two peak concentrations exceeded the MIC for the organism. Treatment with penicillin-G cleared this infection, although subsequent infections with different organisms have required intermittent therapy.

After collection of the final ureteric specimen for urine culture, appropriate oral antibiotic therapy was begun. Six patients were treated with penicillin-G, one with cephaloglycin, and one with nalidixic acid. In each patient, a ureteral catheter of ample size to collect all urine flow was left in place on the affected side and fixed to an indwelling bladder catheter which delivered the urine from the normal kidney. These catheters remained in place for subsequent urine collections for antibiotic excretion studies and renal function tests.

Antibiotic Excretion Studies

Urine specimens were quick-frozen until thawed for antibiotic assay. Urinary antibiotic concentration was determined by large agar plate bioassay using Bacillus subtilis. Urine specimens were diluted to 1:200 with sterile 0.1 normal saline solution and 0.02 ml was placed in prepared wells within the seeded nutrient agar plate. Antibiotic standards ranged from 100 μg per ml down to 6.5 μg per ml. Using a volumetric pipette 0.02 ml of several of these dilutions were inserted into wells on the same agar plate. The solution wells were arranged in four parallel rows, containing counter-linear antibiotic concentrations and diluted urine. The plates were incubated at 37°C (99°F) for 24 hours. Zone size indicating antibiotic activity was measured with a vernier caliper and plotted on semi-log paper against the logarithm of the concentration. This gave a mid-point linear curve between 1 and 100 μg per ml relating the magnitude of the inhibitory zone to the concentration of antibiotic.[4,7]

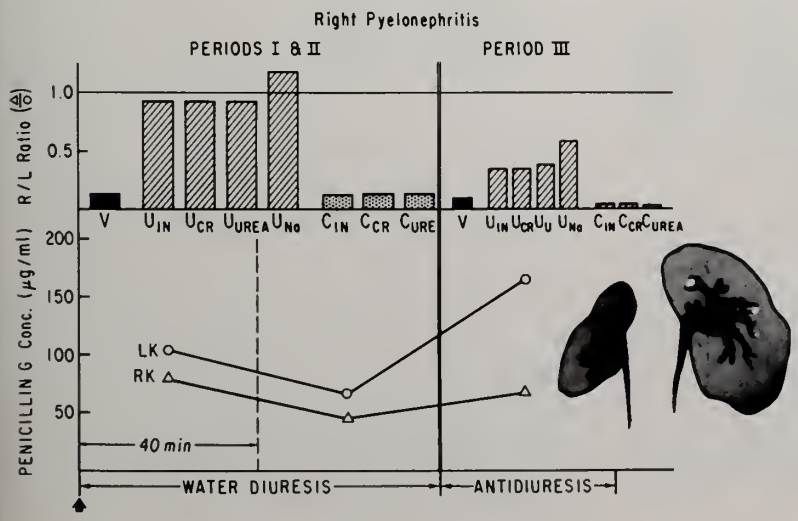


Chart 4.—Documented Right Pyelonephritis. During the first two 40-minute collection periods minimal differences in U_{In}, U_{Cr} and U_{Urea} are shown on the right side along with some impairment in tubular reabsorption of sodium. Penicillin concentration ratios approach those of inulin during these periods but digress during period three when, following emesis, she became antidiuretic and the greater concentrating ability of the left kidney became apparent. Mean concentration of penicillin on the right side was 65 μg per ml (Table 1). This patient was lost to follow-up.

TABLE 1.—*Data on Concentration of Antibiotic in Abnormal and Control Kidney*

Patient and Chart	Antibiotic Used	Mean Urinary Concentration (μg per ml) Abnormal Kidney	Control Kidney	Ratio I/N*
1 ..	Penicillin-G	31	57	0.55
2 ..	Penicillin-G	87	331	0.26
3 ..	Penicillin-G	16	140	0.11
4 ..	Penicillin-G	65	111	0.58
5 ..	Penicillin-G	180	315	0.57
6 ..	Penicillin-G	67	80	0.84
7 ..	Cephaloglycin	706	1,100	0.64
8 ..	Nalidixic Acid	41	123	0.33

*Ratio of infected to normal kidney.

Renal Function Studies

At least three consecutive one-hour urine collection periods were averaged in each patient to arrive at accurate values for differential urinary creatinine concentrations (U_{Cr}) or inulin concentrations (U_{In}). In two patients P-aminohippurate (PAH) was infused at a constant rate to evaluate urinary PAH concentration (U_{PAH}) and clearance (C_{PAH}). Clearances of In, PAH and Cr were calculated where applicable. Urine volumes, concentrations and clearances in each patient were then expressed as a ratio of the measurements on the affected (abnormal) side to those of the opposite (normal) kidney. Studies were performed under varying degrees of hydropenia. No attempt was made to measure maximal urine concentrating ability, but three patients were studied while antidiuretic.

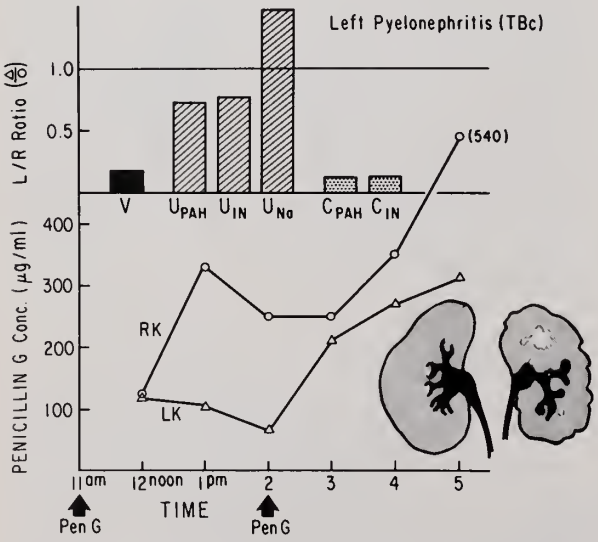


Chart 5.—Patient Uninfected at Time of Study. Urine volumes were significantly reduced from the damaged left kidney with a dramatic defect in tubular reabsorption of filtered sodium compared to the opposite side. Clearances of PAH and In are impaired on the left. Penicillin urinary levels on the left were considerably below those achieved on the right as evidenced by Chart 5 and Table 1.

This patient had been treated for tuberculosis of the urinary tract and was being evaluated for hypertension. Routine and acid-fast cultures were sterile at the time of study.

Results

Mean concentrations of antibiotic in abnormal and control renal urine are listed in Table 1 along with mean ratios of abnormal to control urine concentrations. The specific results of individual patient experiments are included as legends for Charts 1 through 8. To simplify presentation of data, line-drawings of representative urograms in these patients are included with the measurements of their urinary antibiotic concentrations and renal function. Ratios of abnormal to control kidneys have been calculated in each instance to facilitate comparison of data, with urinary concentration ratios at the left and clearance ratios at the right of each diagram. Antibiotic concentrations are plotted in μg per ml and represent the mean concentration achieved in urine from each kidney during the period of collection (usually hourly periods). All patients received antibiotic (800,000 units of penicillin-G before meals, or 250 mg of cephaloglycin or nalidixic acid by mouth) at time indicated by arrows on the abscissa.

Discussion

The renal pathophysiology of unilateral pyelonephritis has been well documented.[8] The medullary defect results in impaired tubular reabsorption of filtered sodium (and obligate water) leading to a decrease in concentration of substances normally excreted in urine on the affected side. Depending on the magnitude of the defect and the extent of nephron damage, urinary sodium concentration (U_{Na}) may actually exceed that in the contralateral kidney (Charts 1, 4 and 5), while U_{Cr}, U_{In}, U_{PAH} and urinary urea concentrations (U_{Urea}) are decreased. These disorders in renal concentration may have little relation to renal plasma flow and glomerular filtration rate (GFR) until substantial losses in nephron unit mass occur. The tubular concentrating defect is most apparent during dehydration, and can be obscured by diuresis. All patients studied had evidence for unilateral functional impairment but in varying degrees. Minimal concentrating differences between kidneys were noted in three pa-

tients (Charts 1, 3 and 4), while more obvious changes were shown in the remaining patients. These variations are probably not significant since all function studies were done under water diuresis. All patients tested had pronounced renal functional impairment on the involved side as measured by comparative clearance studies.

In seven patients substantial differences between the two kidneys were noted in urinary antibiotic concentrations. These concentration differences were often more extreme than differences in U_{Cr} but they represent a truer estimate of maximal tubular function since water diuresis (initiated during the bacteriologic localization study) had been overcome. Maximal urinary concentration of antibiotic on the involved side was never greater than half that achieved in urine from the normal kidney and was one-third or less of the peak normal concentration obtained in six patients. In three of six patients studied during administration of oral penicillin-G, the abnormal kidney failed to achieve the minimal therapeutic concentration of 100 μg per ml (Charts 3, 4 and 6). In two of the remaining patients, peak concentrations were less than 200 μg per ml (Charts 1 and 2). Mean concentrations of antibiotic are perhaps more meaningful since they more closely represent effective therapeutic delivery. Mean urinary concentrations of penicillin-G were less than 100 μg per ml on the abnormal side in five of six patients studied (Table 1).

Maximal urinary concentrating ability was found by Ronald and coworkers[9] to be impaired in patients with proven upper urinary tract infections. They also noted an improvement in overall concentrating ability approaching 100 milliosmols (mosm) per Kg in the majority of those studied after eradication of bacteriuria. That the concentrating defect was reversible may have some application to antibiotic excretion data in the present study. Certainly, impaired urinary antibiotic excretion in active pyelonephritis may be related to acute tubular damage. In four of these patients, however, no active renal infection was documented and yet all had decreased antibiotic excretion on the involved side, consistent with renal tubular disease.

Renal clearance of penicillin-G has been esti-

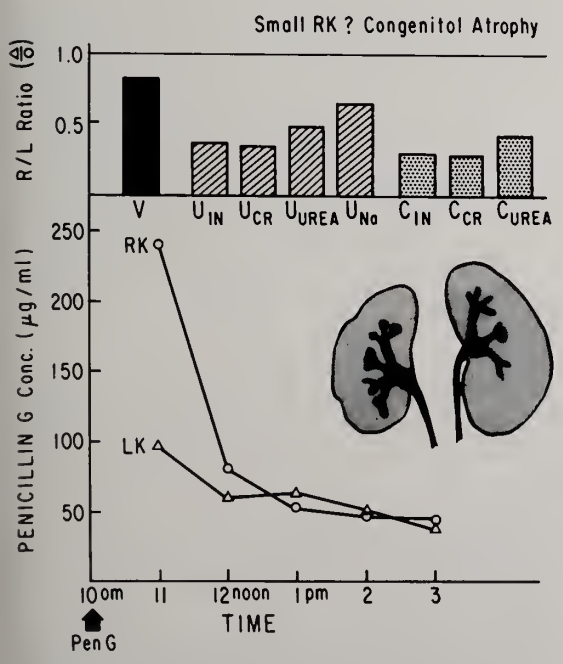


Chart 6.—Patient Uninfected at Time of Study. A substantial impairment in renal tubular function is present on the right side, evidenced by low right to left ratios for the various parameters. Renal clearances are similarly decreased. Penicillin-G concentration in urine from the damaged right kidney fails to approach the peak concentration achieved on the left side after oral administration. Mean concentrations of antibiotic were 67 μg per ml on right and 80 μg per ml on left (Table 1).

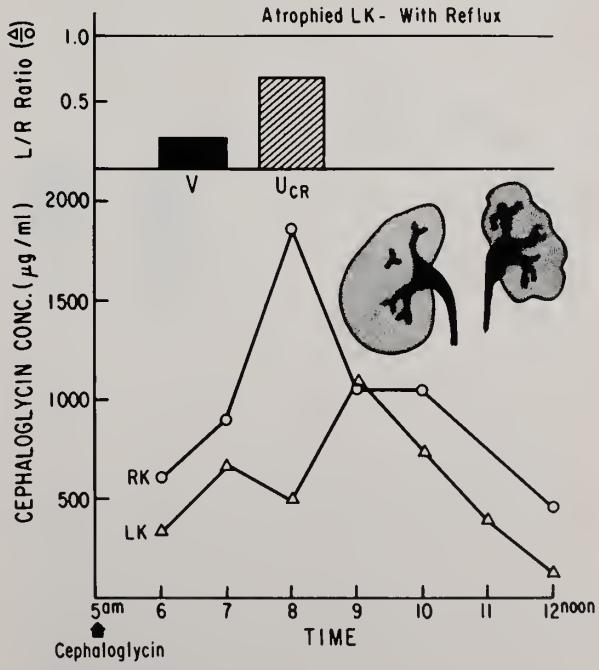


Chart 7.—Infection Localized to Bladder. Urine volume was low with a decrease in U_{Cr} from the structurally abnormal left kidney in this unilaterally refluxing patient. Peak antibiotic concentration was higher and occurred earlier in tests of the urine from the right kidney. Mean concentration on the left was less than two-thirds of that on the right (Table 1).

mated in excess of 380 ml per minute per 1.73 square meters of body surface area.[10] Since this figure exceeds that for GFR, tubular excretion plays a prominent role in delivery of this antibiotic to the urine. It follows that medullary damage from recurrent pyelonephritis will impair urinary antibiotic concentration not only by presenting a more dilute urine to the collecting duct, but by interfering with the usual tubular mechanism of penicillin excretion. In these patients, all with unilateral structural pyelonephritis, substantial defects in penicillin, sodium cephaloglycin and nalidixic acid excretion on the involved side have been shown. Excretion of antibiotic in the urine from the abnormal kidney ranged from 84 percent down to only 11 percent of the urine concentrations achieved in the control kidney. Charts 1 through 8 also suggest a relatively fixed antibiotic excretion capacity on the abnormal side along with the low concentrations. Although it is not specifically proven by these data, one might suspect that administration of larger doses of antibiotic would only result in increased urine levels from the control kidnev.

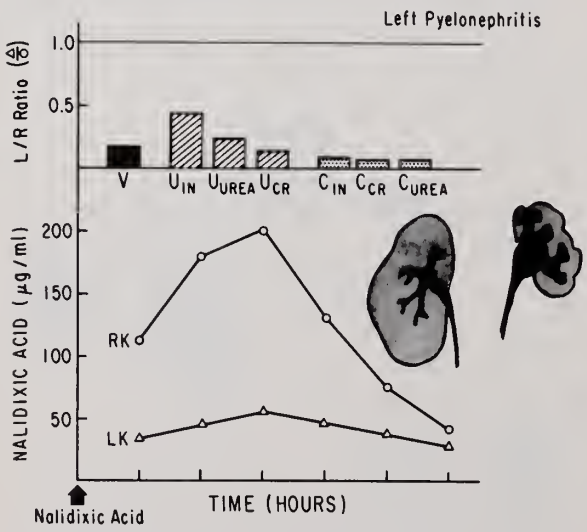


Chart 8.—Documented Left Pyelonephritis. Differential renal function studies show relative tubular impairment on the left with decreased concentrating ability. The clearance ratios indicate the insignificant contribution of the left kidney to total renal function. Maximal urinary concentration of nalidixic acid is achieved in three hours, but the abnormal left kidney reaches only one-fourth the magnitude of that on the right side. Mean antibiotic concentration on the left was 41 μg per ml (Table 1).

P. mirabilis was isolated from the renal urine. Because of penicillin allergy, nalidixic acid was selected (MIC = 25 μg per ml). The mean antibiotic concentration of 49 μg per ml exceeded the MIC and therapy was successful although subsequent repeated infections with different organisms have resulted in nephrectomy.

In the three infected patients where these data are significant (patients 2, 3 and 8), there was an indeterminant relationship of the urinary levels achieved to cure. In patient 2, pyelonephritis persisted with the same generic organism maintaining a similar sensitivity pattern despite urinary antibiotic concentrations in excess of the MIC. In patient 8, the urinary levels of penicillin exceeded the relatively low MIC for the organism (*P. mirabilis*) and treatment was initially effective. In patient 3, however, the infection was cured despite mean urinary antibiotic concentrations from the involved kidney well below the MIC for the organism (two peak concentrations exceeded this figure, however). Clearly, it is necessary to evaluate a larger number of patients before the relationship of impaired antibiotic excretion in unilateral pyelonephritis to the cure of parenchymal infection can be fully appreciated.

Finally, two patients required nephrectomy for ultimate control of morbidity from infection. While some observers would consider such an ablative procedure extreme in pyelonephritis, in well documented cases of recurrent unilateral infection where the involved side contributes only marginally to total renal function, surgical cure of infection is impressive and sustained. The impairment in antibiotic excretion from the involved kidney shown in these patients documents a possible cause for therapeutic failure in unilateral parenchymal disease. Because of this defect in urinary concentration, the use of penicillin-G (and other antibiotics which depend upon high urinary concentration rather than serum levels for cure) may not always be of therapeutic value in unilateral structural pyelonephritis.

REFERENCES

1. Anderson KN, Kennedy RP, Plorde JJ, et al: Effectiveness of ampicillin against gram negative bacteria. JAMA 187:555-561, 1964

2. Brumfit W, Percival A, Carter MJ: Treatment of urinary tract infections with ampicillin—A clinical trial. Lancet 1:130-133, 1962

3. Hoeprich PD: The penicillins, old and new. Calif Med 109: 301-308, 1968

4. Palmer JM, Neal JF, Stamey TA: The use of oral sodium benzylpenicillin in the urinary tract—A study of urinary levels and in vitro activity. Proc of the 6th Int'l Congr of Chemotherapy, Univ of Tokyo Press 1:902-909, 1970

5. Hulbert J: Urinary tract infections and oral penicillin-G. J Clin Path 25:73-75, 1972

6. Stamey TA, Govan DE, Palmer JM: The localization and treatment of urinary tract infections—The role of bactericidal urine levels as opposed to serum levels. Medicine 44:1-36, 1965

7. Bennett JV, Brodie JL, Benner EJ, et al: Simplified accurate method for antibiotic assay of clinical specimens. Applied Microbiology 14:170-177, 1966

8. Stamey TA, Pfau A: Some functional, pathologic bacteriologic, and chemotherapeutic characteristics of unilateral pyelonephritis in man—I. Functional and pathologic characteristics. Invest Urol 1:134-161, 1963.

9. Ronald AR, Cutler RE, Turch M: Effect of bacteriuria on renal concentrating mechanisms. Ann Intern Med 70:723-733, 1969

10. Tuano SB, Johnson LD, Brodie JL, et al: Comparative blood levels of hetacillin, ampicillin, and penicillin-G. N Engl J Med 275:635-639, 1966

Specialty Conference

Moderator
DAVID T. IMAGAWA, PhD

Discussants
MILAN FIALA, MD
JOSEPH W. ST. GEME, JR., MD
TERRY YAMAUCHI, MD
DAVID T. IMAGAWA, PhD

This is a transcription of one of the regular teaching conferences in Infectious Diseases held weekly at Harbor General Hospital, Torrance, California. It has been edited by Doctors Jerrold A. Turner, John Z. Montgomerie, Anthony W. Chow, Thomas T. Yoshikawa and Lucien B. Guze.

Refer to: Imagawa DT, Fiala M, St. Geme JW Jr, et al: Viral infections of the fetus—Teaching Conference, University of California, Los Angeles, and Harbor General Hospital, Torrance (Specialty Conferences). West J Med 120:369-375, May 1974

Viral Infections of the Fetus

DAVID T. IMAGAWA, PH D:* Knowledge pertaining to virus infection of the human fetus is relatively meager. There was a time when viral infections during pregnancy were regarded as the principal cause of congenital malformation. This concept has not been substantiated, for in many instances newer modern virological techniques have failed to incriminate viruses as causing congenital malformations. It has been known for many years that certain virus infections during pregnancy might cause fetal death or stillbirth, but except for cytomegaloviruses and rubella, there is no conclusive evidence that other viruses are important causes of congenital malformation in humans.

Much remains to be learned about the important problem of viral infections of the fetus. The present report summarizes some of the pertinent information currently available. An overview of the problem will be discussed first, followed by comments concerning the biological sequelae in the human fetus, and then methods for prevention and control of fetal infections. Finally, laboratory animal experiments, which may lead to better understanding of the disease processes by which viral agents produce malformation or abnormal function will be described.

From Divisions of Infectious Diseases, Departments of Pediatrics and Medicine, UCLA School of Medicine, Harbor General Hospital.

*Professor of Pediatrics and Microbiology-Immunology, UCLA School of Medicine; Director, Pediatric Research Laboratory, Harbor General Hospital.

Reprint requests to: D. T. Imagawa, Ph.D., Department of Pediatrics, Harbor General Hospital, 1000 West Carson Street, Torrance, CA 90509.

An Overview

MILAN FIALA, MD:† The role of intrauterine viral infections in causing congenital malformations has been previously defined so far only with cytomegalovirus[1,2] and rubella[3,4] although herpes simplex, mumps, influenza, varicella, vaccinia, Coxsackie B, and other viruses (either wild or attenuated vaccine strains) may be surmised to play a role in isolated cases. The incidence of virus infections in pregnancy is affected by the communicability of a particular virus, by the environmental situation and by humoral and cellular defenses of the mother. Several incompletely understood factors influence the transmission of virus from the mother to the fetus and the development of congenital malformations:

- The timing of infection during pregnancy (with rubella the maximum risk of heart and ocular abnormalities is present during the first two months).
- Absence of maternal immunity (the presence of any maternal hemagglutination-inhibiting, neutralizing or complement-fixing antibody protects

†Assistant Professor of Medicine, UCLA School of Medicine, Division of Infectious Diseases, Department of Medicine, Harbor General Hospital.

the fetus from rubella; the role of maternal cytomegalovirus antibody in protection of the fetus is not clear at present, although it has been proposed that cytomegalic inclusion disease occurs only when cytomegalovirus infection is primary[5] but not when it represents reactivation of a latent cervical infection of the mother.[6]

- Barrier function of the placenta.
- Immunological competence of fetus.

The viruses known or suspected to cause congenital abnormalities belong to different groups with widely different characteristics, including type of nucleic acid, structure and composition of virus capsid and interactions with host cells which range from mitogenic inhibition with rubella to lytic infection with Coxsackie B viruses.

Unlike cytomegalovirus infection, fetal infection with rubella virus often has severe consequences. The range of malformations due to rubella is very wide and probably due to the propensity of rubella virus to inhibit mitotic cell division. Major manifestations[7] include congenital heart disease, hearing loss due to damage to the inner ear, retinopathy and cataract (well known since the pioneering work of Gregg on the incidence of congenital blindness in relation to rubella epidemics[8]). During the neonatal period thrombocytopenic purpura or hepatitis and, later on, psychomotor retardation may develop.

In congenital cytomegalic inclusion disease—the most severe form of cytomegalovirus infection of fetus, probably acquired during the first 20 weeks of pregnancy—the most frequent congenital abnormality is microcephaly but other forms of neural and possibly extraneural (first arch and heart) abnormalities also occur. Most cytomegalovirus infections of the fetus are, however, asymptomatic or subtle, manifested by progressive developmental and mental retardation. Hepatosplenomegaly or hepatitis may be found at birth or develop postnatally.

Clinical and laboratory findings such as microcephaly, chorioretinitis and periventricular calcifications may suggest cytomegalovirus involvement; "pepper and salt" fundi or patent ductus arteriosus strongly point to congenital rubella. However, because of the similarity of clinical manifestations within the "TORCH" (toxoplasma, other viruses and syphilis, rubella, cytomegalovirus and herpes simplex virus) complex, specific diagnosis must be made by laboratory methods:

1. Virus isolation—virus infection may be chronic with prolonged virus excretion.

2. Antibody response—

(a) In the newborn: elevated IgM-globulin levels ($\geq$18 mg per 100 ml) are suggestive of a congenital infection.[9] Detection of specific IgM antibody to cytomegalovirus,[10] rubella virus, or toxoplasma in cord blood are considered as conclusive evidence for the role of each agent.

(b) Postnatally: in congenitally infected children specific IgG antibodies are rising while in children who acquired antibody passively from the mother the antibody titers are falling.

3. Histopathologic techniques—presence of large cells with intranuclear inclusions are characteristic of cytomegalovirus infection.

Biological Disturbances

JOSEPH W. ST. GEME, JR., MD:* Ordinarily one thinks of anatomical defects and embryogenetic anomalies when considering the impact of intrauterine viral infections in man. However, the physiologic and biologic sequelae of fetal viral infections are important, are poorly understood, and are more subtle than are gross, structural abnormalities. The pathogenetic mechanisms of the structural and biological abnormalities in the fetus include vascular, cellular, and placental factors. For example, rubella virus presumably replicates in the endothelial cells of the major and minor vasculature, inducing vascular injury and impairment of blood flow to differentiating and developing tissues.[11] The nucleic acid and protein metabolism of infected cells may be altered by some viruses with resultant diminution of cellular replication and possibly function.[12,13] If gestational viral infections modify either the development or the anatomic integrity of the placental vasculature, as well as the constituency and biochemical function of the intrinsic cellular population of the placenta, one could envision a profound impact on placental function and consequent fetal development.

An epidemiologic perspective of potential fetal viral infections is important. By no means are maternal infections with the two major viral pathogens rare. The incidence of rubella during pregnancy is ordinarily about 0.1 percent.[14] During the 1964-1965 epidemic the incidence was 2 percent. Approximately 5 percent of women develop rising titers of cytomegalovirus antibody during pregnancy and an astonishing 1 percent of newly born infants shed the virus in their urine.[14,15] The major

*Professor of Pediatrics, UCLA School of Medicine, Chairman, Department of Pediatrics, Harbor General Hospital.

source of perinatal cytomegalovirus infection may be third trimester transplacental maternal viremia, perhaps ascending transcervical infection, or the viral exposure of vaginal delivery, since 12 to 28 percent of pregnant women shed this virus in their cervical secretions during the late phase of gestation.[16,17] We suspect that the more frequent *late* fetal cytomegalovirus infection is also more benign than transplacental infection during *early* pregnancy.

Growth Retardation

One of the most striking sequelae of gestation viral infection is diminished fetal growth. Fetal growth retardation may be the only manifestation of congenital rubella virus and cytomegalovirus infection. Postnatal growth is also impaired, as is true for infants who have incurred fetal stunting for other reasons. Ultimately, in the absence of structural and functional abnormalities of the brain and heart, one might predict that the majority of these infants should attain nearly normal stature. Michaels and Kenny[18] made careful sequential observations of infants congenitally infected with rubella virus. They reported that these infants possessed no endocrine abnormalities and began to accelerate their growth when rubella virus disappeared from their tissues between six and twelve months of age. We need many more data of this sort. Several of the large centers which documented substantial numbers of young infants with the congenital rubella syndrome in 1964 may be able to provide information about subsequent growth, eight to ten years later.

The most crucial gauge of fetal and postnatal development is cerebral growth. Head circumference is also reduced by transplacental rubella virus and cytomegalovirus infection.[18-20] In some instances, profound microcephaly occurs, particularly in infants afflicted with more severe, generalized fetal cytomegalovirus infection. Not enough data are available to predict the rate of restoration of head circumference of mildly affected infants to normal dimensions during the early years of life.

Naeye[21,22] demonstrated that the diminished weight of fetal organs with congenital rubella virus and cytomegalovirus infections is due to decreased numbers of cells in the tissues rather than to a reduction in the size of cells. Unfortunately, available data are inadequate to determine whether the same is true for the placenta. Rawls and Melnick[13] cultivated the tissues of rubella virus-infected embryos and observed an impressive limitation in rates of cellular replication when compared with normal tissues. Furthermore, Plotkin and Vaheri[23] demonstrated an inhibitor substance elaborated by virus-infected cells which curbed the multiplication of normal cells. Although the presence of this inhibitor has not been substantiated by other investigators, it offers a logical explanation for the otherwise remarkable fact that the size of an organ may be decreased, yet only 0.1 percent of the cells contain rubella virus.[24]

It is conceivable that the vasculopathic components of gestational rubella virus infection exert a deleterious effect on the nutrition of embryonic and fetal tissues, with consequent attenuation of cellular division. The direct cellular and vascular aspects of placental infection may suffice to produce placental dysfunction. The relationship between placental insufficiency and fetal malnutrition is well known. Ordinarily, the disturbance of growth is limited to weight alone. Placental dysfunction is also associated with hypoglycemia and hypocalcemia. These two metabolic disturbances have not been described with fetal rubella virus and cytomegalovirus infections. Extrapolating from these other experiments of nature, one might conclude that the fetal growth retardation of these gestational viral infections cannot be attributed to a primary disturbance of placental function.

Neurologic Sequelae

The devastating neurologic effects of congenital rubella virus and cytomegalovirus infection are well known. Encephalitis, persistent replication of virus in the brain, intracranical calcifications, and severe microcephaly constitute the signal features of overt neural infection, frequently incompatible with survival. The more compelling concern is the potential intellectual aftermath of the more subtle cerebral involvement of relative microcephaly. A substantial percentage of children with microcephaly as the only apparent early manifestation of congenital cytomegalovirus infection are obviously retarded when evaluated carefully during the immediate preschool years.[2] However, one should not conclude that all children afflicted with intrauterine viral infection are doomed to a future of intellectual inadequacy. Children with congenital cytomegalovirus infection who appear normal at birth and at one year have been shown to possess intellectual competence similar to that of

their cultural peers at four years of age.[25] A recent study of a large number of children with congenital rubella, including some with prior fetal growth retardation, small stature, and microcephaly, disclosed a normal distribution of mental function.[26]

A fascinating, but tragic, element of the encephalopathy of transplacental rubella virus infection, recognized only very recently, is infantile autism.[27] This observation opens exciting new elements of speculation concerning this perplexing and serious behavioral disorder. Some children may have no other manifestations of transplacental rubella virus infection with this psychopathic condition.

Immunologic Deficiency

Profound maturational defects of immunoglobulin synthesis have been described with congenital rubella virus infection. Hypergammaglobulinemia and dysgammaglobulinemia have occurred in combination with the usual anatomic abnormalities.[28,29] More subtle immunobiologic perturbations have been detected by Michaels.[30,31] Rubella virus-infected infants are unable to produce the anticipated titers of antibody to the traditional immunizing biologicals of childhood. When rubella virus disappears from the pharynx and urine of these infants, the capacity to marshal an appropriate antibody response appears. There also exists a transient deficit in the expression of cell-mediated immunity or delayed hypersensitivity.[31-33] Since other natural and experimental viral infections shut off normal humoral and cellular immunity, it should not be surprising that a transplacental viral infection, with persistence of virus replication throughout several months of postnatal life, may also interfere with B-cell and T-cell function.[34] Although more data are required, infants congenitally infected with cytomegalovirus are adequately immunoresponsive to diphtheria toxoid.[31]

Altered Hematopoiesis

Because of the similarities between hematopoietic and immunopoietic cellular development, it is of more than passing interest that extramedullary hematopoiesis has been described in the skin of infants with congenital rubella virus and cytomegalovirus infection.[35] Inadequate immunocellular coping with persistent fetal virus infection may provoke a distorted proliferation of primitive stem cells as an alternate immunoresponsive cell population. It is intriguing that rare histocytic reactions and lesions have been described with both congenital rubella virus and cytomegalovirus infections.[36,37]

In 1941, Gregg[8] described the association of cataracts with congenital rubella. Soon thereafter, the sequelae of transplacental rubella virus infection were recognized as the classic tetrad of cataracts, patent ductus arteriosus, deafness and microcephaly. In 1964, the expanded rubella syndrome was delineated; it included, as newly or more clearly recognized manifestations, hepatosplenomegaly, thrombocytopenia purpura, metaphysitis, encephalitis, peripheral pulmonic artery stenosis, interstitial pneumonia, hepatitis, and intrauterine growth retardation.[4] Several years later, less obvious sequelae of fetal rubella virus infection emerged as clinicians began to look for distortion of physiologic function rather than merely anatomic defects. In the late 1950's, when the more definitive virologic and clinical studies of congenital cytomegalovirus infection were undertaken, the disease loomed as a rare, diffuse, devastating, and usually fatal process.[1] It is obvious now, almost 20 years later, that these early observations were focused only on the top of the pathophysiologic iceberg.

Proposed Solutions

TERRY YAMAUCHI, MD:* For the past three decades scientists have sought the best method to prevent, control, or treat viral infections of the human fetus. More productive investigation is needed for effective treatment of the maternal infection or the congenitally infected fetus. At present, the antiviral agents available make this course unfeasible. Drugs such as iodo-deoxyuridine and cytosine arabinoside effectively prevent replication of DNA viruses *in vitro*.[38] However, the very nature of their action, the inhibition of nucleic acid synthesis, precludes their use in a pregnant woman or fetus with actively dividing cell populations. An antiviral agent which will inhibit or destroy only the infecting virus and spare the normal host cells would be ideal.

Another method of controlling viral infections is early diagnosis of maternal infection followed by selective abortion of the exposed fetus. If a pregnant woman has an overt illness, such as rubella, the diagnosis is relatively easy. However, often there is only a history of a mild, non-specific illness, a cytomegalovirus infection, or recent

*Assistant Professor of Pediatrics, UCLA School of Medicine, Chief, Division of Ambulatory Pediatrics, Department of Pediatrics, Harbor General Hospital.

exposure to rubella. In these cases the current techniques to establish the diagnosis of a specific viral infection are of primary importance. The techniques include: Recovery of virus in the gravid woman from blood, throat or urine, ideally from the blood to document a viremia; or serological studies demonstrating a change in specific antibody titer. Serological studies are imperative in the management of a pregnant woman recently exposed to rubella. The patient with pre-existing antibodies is less susceptible to infection than is one who is sero-negative. Amniocentesis and the development of assay systems to aid diagnosis of inborn errors of metabolism[39] support the hope that intrauterine viral infections might be evaluated in a similar fashion.

The most effective solution to the problem of viral infections of the human fetus is to prevent the primary maternal infection. Methods of preventing infection in pregnant women include isolation from infectious diseases and the improvement of maternal immunologic defense mechanisms. To isolate all pregnant women or women about to become pregnant would be impossible. The improvement of maternal immunity is a field of active research today. The use of viral vaccines in a widespread immunization program is a logical approach to improving maternal resistance to fetopathic viruses. Such a program has been initiated to control rubella virus infection. The problems of using live, attenuated viral vaccines are well illustrated by the controversial rubella vaccine.[40,41] The purpose of the rubella vaccine is to protect the unborn fetus from rubella virus infection and consequent deformities. At present, this vaccine is the only immunization that is given not to protect the recipient from disease, but to protect a fetus which may not be conceived for many years after the vaccine is administered. Clinical investigation has substantiated the effectiveness of this vaccine in preventing overt illness.[42,43] It is logical to believe that vaccinating the mother will protect the fetus from rubella infection. But this may not be true. While the vaccine protects the woman from overt disease, a few subclinical infections have been reported.[44] These subclinical cases may harbor and shed the wild rubella virus without the clinical manifestations of the disease. However, viremia and subsequent infection of the fetus has not yet been demonstrated in such persons.

The duration of immunity following rubella vaccination is another unknown quantity. Though it appears to be long-lasting, it has not been studied long enough to substantiate unwavering durability. Some clinicians are concerned with the possibility that girls being vaccinated today will develop low titers of rubella antibody in the future and become susceptible to re-infection. An even greater fear is the possibility that low antibody titer will mask rubella infection, setting the stage for an epidemic of subclinical infections with a population of girls approaching the child-bearing age.

The effects of live, attenuated vaccines on the human fetus are unknown. Rubella vaccine in particular is contraindicated in pregnancy because of its potential teratogenicity.[45] In some cases women who inadvertently received rubella vaccine during early gestation and lacked serum antibody to the virus had therapeutic abortions because of the possibility of delivering a congenitally deformed infant. Teratogenicity in humans, however, has never been shown with attenuated strains of viruses, although the viruses have been recovered from the cervix, placenta, and fetus.[41,46,47] In animal models, attenuated strains of viruses have been shown to induce congenital malformations (see next section on animal models).

One of the goals of massive immunization programs has been the development of herd immunity. Theory suggests that if enough people are "immune" to rubella via vaccination, the natural disease would not spread. The effectiveness of this theory has been questioned. Studies involving closed populations, such as military recruits and retarded children in institutions, revealed that when 60 to 90 percent of the population were immunized, the susceptible individuals within the group nevertheless had rubella during epidemic periods.[48,49] Therefore, in order for herd immunity to be protective, if possible at all, even larger numbers of people would have to be immunized.

In summary, the management of viral infections of the human fetus requires early diagnosis, development of safe antiviral chemotherapy and a comprehensive immunization program with effective vaccines.

Animal Models

Dr. Imagawa: As was pointed out earlier, knowledge of viral infections of human fetus is meager but examples of congenital infections of viral origin in domestic and experimental animals are

expanding in number. Through work with these animal models, information leading to better understanding of the pathogenesis of virus infections which produce malformations is being acquired. Such information should be helpful in developing methods to prevent teratogenic viral infections in man.

Listed in Tables 1 and 2 are examples of congenital viral infections in domestic and experimental animals. Of particular interest in the animal model systems are the two attenuated viruses which are ordinarily used for immunizations of the animals. Hog-cholera virus, a RNA myxovirus, attenuated by passage in rabbits, is an effective immunogen in an adult animal, but can cause abnormal litters when given to a pregnant sow.[50] In animals receiving vaccine viremia develops and transplacental infection may occur. Piglets from mothers receiving the live vaccine have anomalies of the kidneys, nose and central nervous system. The importance of adequate immunity in the prevention of transplacental infection was recently described.[70] Transplacental infection did not occur in sows which had antibody titers of 1:2 or greater at the time of inoculation with the attenuated hog cholera virus. On the other hand, transplacental passage of the virus was demonstrated in sows that were previously vaccinated but lacked evidence of neutralizing antibodies. Furthermore, the authors strongly recommended that contact between susceptible pregnant sows and recently vaccinated animals should be avoided.

Similarly, attenuated blue-tongue virus of sheep, a RNA arbovirus, given to the pregnant ewe produces multiple malformations and brain hypoplasia of her lamb.[51] It is a depressing fact that attenuated viruses which are used for immunizations and produce no virulent effects in adult animals can be so deleterious to the fetus. It is with this fact in mind that stringent precautions are urged to make sure that live attenuated rubella virus or any other live vaccine virus is not administered, intentionally or by accident, to pregnant women.

REFERENCES

1. Weller TH, Hanshaw JB: Virologic and clinical observations on cytomegalic inclusion disease. N Engl J Med 266:1233-1244, 1962.

TABLE 1.—*Congenital Viral Infections in Domestic Animals*

Virus	*Host*	*Effects*	*References*
Attenuated hog cholera virus	Swine	Fetal death and multiple malformations	Sautter, J.H., et al.[50]
Attenuated blue-tongue virus	Sheep	Fetal death, multiple malformations, brain hypoplasia	Schultz, G. and DeLay, P.D.[51]
Bovine parainfluenza[3]	Bovine	Fetal death	Sattar, S.A., et al.[52]
Bovine viral diarrhea-mucosal disease virus	Bovine	Fetal death	Alafson, P., et al.[53]
Bovine rhinotracheitis	Bovine	Fetal death	Lukas, G.N., et al.[54]
Feline panleukopenia virus	Cat	Cerebellar hypoplasia	Kilham, L., et al.[55]
Feline herpesvirus	Cat	Fetal death	Hoover, E.A. and Griesemer, R.A.[56]
Equine rhinopneumonitis virus	Horse	Fetal death	Domock, W.V.[57]

TABLE 2.—*Congenital Viral Infections in Experimental Animals*

Virus	*Host*	*Effects*	*References*
Rubella	Rabbit	Transplacental infection	Belcourt, R.J.P., et al.[58]
		Growth retardation and malformations	Kono, R., et al.[59] London, W.T., et al.[60]
	Monkey	Transplacental infection	Parkman, P.D., et al.[61]
		Growth retardation and ocular changes	Delahunt, C.S. and Rieser, N.[62]
	Rat	Growth retardation, heart and ocular changes	Cotlier, E., et al.[63]
	Ferret	Cerebrovascular lesions	Rorke, L.B., et al.[64]
Mumps	Chick and monkey	Growth retardation, dysgammaglobulinemia and cardiomyopathy	St. Geme. J.W., Jr. et al.[65,66,67]
Rat virus and minute virus of mice (picodna)	Rat, hamster, and mouse	Fetal death and cerebellar hypoplasia	Kilham, L. and Margolis, G.[68,69]

2. Hanshaw JB: Congenital cytomegalovirus infection: A fifteen year perspective. J Infect Dis 123:555-561, 1971

3. Alford CA Jr, Neva FA, Weller TH: Virologic and serologic studies on human products of conception after maternal rubella. N Engl J Med 271:1275-1281, 1964

4. Rubella Symposium. Am J Dis Child 110:345-476, 1965

5. Diosi P, Streza I, Dan E: Les infections intra-uterines a virus cytomegalique. Gync Obst (Paris), 68:259-264, 1969

6. Montgomery R, Youngblood L, Medearis DN Jr: Recovery of cytomegalovirus from the cervix in pregnancy. Pediatrics 49: 524-531, 1972

7. Cooper LZ, Krugman S: Clinical manifestations of postnatal and congenital rubella. Arch Opthal 77:434-439, 1967

8. Gregg NM: Congenital cataract following German measles in the mother. Trans Opthal Soc Australia 3:35-46, 1941

9. Alford CA, Blankenship WJ, Straumfjord JV, et al: The diagnostic significance of IgM-Globulin elevations in newborn infants with chronic intrauterine infections, *In*: Birth Defects Original Article Series. New York, The National Foundation, 1968, pp 3-19

10. Hanshaw JB, Steinfeld HJ, White CJ: Fluorescent-antibody test for cytomegalovirus macroglobulin. N Engl J Med 279:566-570, 1968

11. Tondury G, Smith DW: Fetal rubella pathology. J Pediat 68:867-879, 1966

12. Moore NF, Lomniczi B, Burke DC: The effect of infection with different strains of Newcastle disease virus on cellular RNA and protein synthesis. J Gen Virol 14:99-101, 1972

13. Rawls WE, Melnick JL: Rubella virus carrier cultures derived from congenitally infected infants. J Exp Med 123:795-816, 1966

14. Sever JL: Perinatal infections affecting the developing fetus and newborn, *In* The Prevention of Mental Retardation Through Control of Infectious Diseases. Public Health Service Publication, No. 1692, 1968, pp 37-68

15. Starr JG, Bart RD Jr, Gold E: Inapparent congenital cytomegalovirus infection. N Engl J Med 282:1075-1078, 1970

16. Reynolds DW, Stagno S, Hosty TS, et al: Maternal cytomegalovirus excretion and perinatal infection. N Engl J Med 289:1-5, 1973

17. Numazaki Y, Yano N, Morizuka T, et al: Primary infection with human cytomegalovirus: Virus isolation from healthy infants and pregnant women. Am J Epidem 91:410-417, 1970

18. Michaels RH, Kenny FM: Postnatal growth retardation in congenital rubella. Pediatrics 43:251-259, 1969

19. Lundstrom R: Rubella during pregnancy. Act Pediat 51: suppl 133, 1962

20. Hanshaw JB: Cytomegalovirus complement-fixing antibody in microcephaly. N Engl J Med 275:476-479, 1966

21. Naeye RL, Blanc W: Pathogenesis of congenital rubella. JAMA 194:1277-1283, 1965

22. Naeye RL: Cytomegalic inclusion disease. Am J Clin Path 47:738-744, 1967

23. Plotkin SA, Vaheri A: Human fibroblasts infected with rubella virus produce a growth inhibitor. Science 156:659-661, 1967

24. Rawls WE, Desmyter J, Melnick JL: Virus carrier cells and virus-free cells in fetal rubella. Proc Soc Exp Biol 129:477-483, 1968

25. Kumar ML, Nankervis GA, Gold E: Inapparent congenital cytomegalovirus infection: A follow-up study. N Engl J Med 288: 1370-1372, 1973

26. Boyd RD, MacFarlane DW: Intrauterine rubella and intellect. Clin Res 20:270, 1972

27. Chess S: Autism in children with congenital rubella. J Autism Child Schiz 1:33-47, 1971

28. Plotkin SA, Klaus RM, Whitely JP: Hypogammaglobulinemia in an infant with congenital rubella syndrome: Failure of 1-adamantanamine to stop virus secretion. J Pediat 69:1085-1091, 1966

29. Hancock MP, Huntley CC, Sever JL: Congenital rubella syndrome with immunoglobulin disorder. J Pediat 72:636-645, 1968

30. Michaels RH: Immunologic aspects of congenital rubella. Pediatrics 43:339-350, 1969

31. Michaels RH: Suppression of antibody response in congenital rubella. J Pediat 80:583-588, 1972

32. Olson GB, Dent PB, Rawls WE, et al: Abnormalities of in vitro lymphocyte responses during rubella virus infections. J Exp Med 128:47-68, 1968

33. White LR, Leikin S, Villavicencio O, et al: Immune competence in congenital rubella—Lymphocyte transformation, delayed hypersensitivity, and response to vaccination. J Pediat 73:229-234, 1968

34. Notkins AL, Mergenhagen SE, Howard RJ: Effect of virus infections on the function of the immune system. Ann Rev Microbiol 24:525-538, 1970

35. Brough AJ, Jones D, Page RH, et al: Dermal erythropoiesis in neonatal infants. Pediatrics 40:627-635, 1967

36. Claman HN, Suvatte V, Githens JH, et al: Histocytic reaction in dysgammaglobulinemia and congenital rubella. Pediatrics 46:89-96, 1970

37. Balfour HH Jr, Speicher CE, McReynolds DG, et al: Juvenile xanthogranuloma associated with cytomegalovirus infection. Am J Med 50:380-384, 1971

38. Buthala DA: Cell culture studies on antiviral agents—I. action of cytosine arabinoside and some comparison with 5-iodo-2-deoxyuridine. Proc Soc Exp Biol Med 115:69-77, 1964

39. Abdul-Karim RW, Beydown SN: Amniotic fluid—The value of prenatal analysis. Postgrad Med 52:147-149, 1972

40. Leedom JM, Wilkins J, Portnoy B, et al: Important assumptions, extrapolations, and established facts which underlie the use of live rubella virus vaccine. Am J Epidemiol 92:151-157, 1970

41. Larson HE, Parkman PD, Davis WJ, et al: Inadvertent rubella virus vaccination during pregnancy. N Engl J Med 284:870-873, 1971

42. Meyers HM Jr, Parkman PD: Rubella vaccination—A review of practical experience. JAMA 215:613-619, 1971

43. Wyll SA, Grand MG: Rubella in adolescents, serologic assessment of immunity. JAMA 220:1573-1575, 1972

44. Wilkins J, Leedom JM, Portnoy B, et al: Reinfection with rubella virus despite live vaccine induced immunity: Trials of HPV-77 and HPV-80 live rubella virus vaccines and subsequent artificial and natural challenge studies. Am J Dis Child 118:275-294, 1969

45. Prelicensing statement on rubella virus vaccine. Morbidity Mortality Weekly Rep 18:124-125, 1969

46. Vaheri A, Vesikari T, Oker-Blom N, et al: Isolation of attenuated rubella-vaccine virus from human products of conception and uterine cervix. N Engl J Med 286:1071-1074, 1972

47. Yamauchi T, Wilson C, St. Geme JW Jr: Transmission of live attenuated mumps virus to the human placenta. N Engl J Med 290:710-712, 1974

48. Horstmann DM, Liebhaber H, LeBouvier G, et al: Rubella reinfection of vaccinated and naturally immune persons. N Engl J Med 283:771-778, 1970

49. Farquhar JD: Experience with rubella and rubella immunization in institutionalized children. J Pediat 83:51-56, 1973

50. Sautter JH, Young GA, Luedke AJ, et al: The experimental production of malformations and other abnormalities in fetal pigs by means of attenuated hog cholera virus, *In:* Proc 90th Annual Meeting Amer Vet Med Assoc, 1953, pp 146-150

51. Schultz G, DeLay PD: Losses in newborn lambs associated with blue-tongue vaccination of pregnant ewes. J Am Vet Med Assoc 127:224-226, 1955

52. Sattar SA, Bohl EH, Senturk M: Viral causes of bovine abortion in Ohio. J Am Vet Med Assoc 147:1207-1210, 1965

53. Alafson P, MacCallum A, Fox F: An apparently new transmissible disease of cattle (BVD). Cornell Vet 36:205-213, 1946

54. Lukas GN, Weidenbach SJ, Palmer KG, et al: A bovine viral isolate neutralized by IBR immune serum as a cause of abortion in cattle. Proc 67th Annual Meeting. U.S. Livestock San A 32:108-128, 1963

55. Kilham L, Margolis G, Colby E: Congenital infections of cats and ferrets by feline panleukopenia virus manifested by cerebellar hypoplasia. Lab Invest 17:465-480, 1967

56. Hoover EA, Griesemer RA: Experimental feline herpesvirus infection in the pregnant cat. Am J Pathol 65:173-188, 1971

57. Domock WV: The diagnosis of virus abortion in mares. J Am Vet Med Assoc 96:655-666, 1940

58. Belcourt RJP, Wong FC, Walcroft MJ: Growth of rubella virus in rabbit foetal tissues and cell cultures. Canad J Publ Hlth 56:253-254, 1965

59. Kono R, Hibi M, Hayakawa Y, et al: Experimental vertical transmission of rubella virus in rabbits. Lancet 1:343-347, 1969

60. London WT, Fucillo DA, Sever JL: Growth retardation occurs in rabbits congenitally infected with rubella virus. Proc Intern Symp on Rubella Vaccine. London, 1968, 11:121-124 (Karger, Basel/New York) 1969

61. Parkman PD, Phillips PE, Meyer HM Jr: Experimental rubella virus infection in pregnant monkeys. Am J Dis Child 110: 390-394, 1965

62. Delahunt CS, Rieser N: Rubella-induced embryopathies in monkeys. Am J Obstet Gynec 99:580-588, 1967

63. Cotlier E, Fox J, Bohigian G, et al: Pathogenic effects of rubella virus on embryos and newborn rats. Nature Lond 217:38-40, 1968

64. Rorke LB, Fabiyi A, Elizan TS, et al: Experimental cerebrovascular lesions in congenital and neonatal rubella infections of ferrets. Lancet 2:153-154, 1968

65. St. Geme JW Jr, Peralta H, Farias E, et al: Experimental gestational mumps virus infection and endocardial fibroelastosis. Pediatrics 48:821-826, 1971

66. St. Geme JW Jr, Davis CWC, VanPelt LF: Altered growth following gestational viral infection of the placental and aplacental host. Pediat Res 4:460-461, 1970

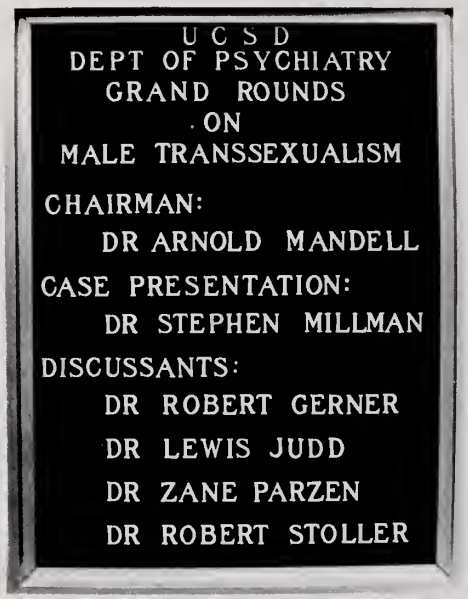
67. St. Geme JW Jr, Davis CWC, Peralta HJ, et al: The biologic perturbations of persistent embryonic mumps virus infection. Pediat Res 7:541-552, 1973

68. Kilham L, Margolis G: Spontaneous hepatitis and cerebellar hypoplasia in suckling rats due to congenital infections with rat virus. Am J Path 49:457-475, 1966

69. Kilham L, Margolis G: Fetal infections of hamsters, rat and mice induced with the minute virus of mice (MVM). Teratology 4:43-61, 1971

70. Stewart WC, Carbrey EA, Kresse JI: Transplacental hog cholera infection in immune sows. Am J Vet Res 33:791-798, 1972

Refer to: Gerner R, Judd L, Mandell A, et al: Male transsexualism—Psychiatric Grand Rounds, University of California, San Diego, and San Diego Veterans Administration Hospital. West J Med 120:376-391, May 1974



Male Transsexualism

Based on Psychiatric Grand Rounds held at the San Diego Veterans Administration Hospital, a teaching facility of the School of Medicine, University of California, San Diego, in September, 1973; edited by Barbara Blomgren, BA, and Leighton Huey, MD.

DR. MANDELL:* Psychiatric intervention once focused primarily on intrapsychic phenomena, but our frontiers have expanded in two directions—into (1) behavioral biology and (2) environmentally-based personality problems. Gambits such as "This person is not a good candidate for psychiatric treatment" are no longer allowable. We must get into areas of need and then function as best we can, learning as we go. Physicians function in part as life-brokers to the deviant. The dying patient, the burned patient, the patient undergoing renal dialysis or kidney transplant—all suffer from frightful impingements of reality and partially stigmatized social roles, no less than those with psychosexual problems. All need help in using their strengths and environmental resources to cope with their difficulties.

Today we bring the techniques of inquiry, conceptualization and therapy to bear on a major and complicated psychosocial problem: the entrapment of a person in a body of the wrong sex. Such a mixture of psychological phenomena and reality (with biological overtones) is a model problem in modern psychiatry that I feel has wide significance for physicians dealing with deviant patients, particularly those who stir strong feelings. We are grateful to Dr. Robert Stoller, who has worked almost his whole creative life studying gender identity, for joining us.

DR. MILLMAN:† The patient is a 20-year-old biological male who presented with a request for a sex-change operation. He was born in upstate California, the younger of two daughters (sic). The family was deserted by the father before the patient was born. Shortly after the patient's birth the mother married a man who had two children. One half-sister to the patient was born of this marriage. The patient remembers the stepfather as cold, distant, and occasionally physically abusive. The patient disliked the stepfather's heavy drinking and his interest only in the younger children in the house. The mother was described by the patient as overly protective, particularly when the patient was four or five years old and showed signs of being effeminate. The patient first remembers feeling like a female around that age when the mother and older sister began dressing him up in women's clothing. This he remembers as a "nice experience." The patient remembers having had throughout his childhood strange feelings about his identity and being interested in feminine concerns such as dolls, playing house, and

*Professor and Chairman, Department of Psychiatry, UCSD.
Reprint requests to: Barbara Blomgren, Editor, Department of Psychiatry, UCSD School of Medicine, La Jolla, CA 92037.

†Resident in Psychiatry, UCSD.

preferring girls to boys as playmates. He felt that this was unacceptable to his family and society and continued to masquerade as a boy. The patient's mother was concerned with keeping his effeminate behavior from her husband, who would hit the child when he noticed such things. The stepfather labelled the boy a "sissy" and a "mother's boy."

Throughout childhood and adolescence the patient maintained a facade of normality. He did well in school and dated occasionally. On one occasion in high school he had sexual intercourse with a girl in the back of a car "because it was expected." The patient said he derived no pleasure from this experience, in fact found it somewhat repulsive. When the patient was in the 11th grade his parents began to drink heavily, and there was much physical abuse in the home. This prompted him to leave home on several occasions. He was finally referred to juvenile authorities who recommended that he enlist in the Navy to "get straightened out." The patient spent six months in the Navy as a hospital corpsman. He found this close contact with men extremely uncomfortable and was able to obtain a discharge for severe anxiety. Upon discharge he met several transsexuals and realized that it would be possible for him to live as a female. Shortly thereafter he began cross-dressing and eventually consulted an endocrinologist. After complete psychiatric evaluation the patient was started on hormonal therapy and is currently taking Estinyl® (Schering) and Delalutin® (Squibb).

She has been on hormonal therapy for approximately two years, with remarkable physical results, including breast development, loss of body hair, atrophy of the testes, and "new physical well-being" including hyperemotionality. She has also undergone rhinoplasty and several facial silicone injections. Until recently the patient supported herself by prostitution, which resulted in a number of arrests with subsequent exposure and ridicule. She has also performed at a discotheque. On one occasion, thrilled at the profound changes associated with endocrine therapy, she exposed her breasts over a highway overpass. Since then the patient has become comfortable with her appearance as a female and there have been no further episodes of exhibitionism.

She recently met a young serviceman whom she dated for a few months before he learned that she was male. In spite of this they were married approximately one month ago, and he was shipped overseas. The patient is currently living as a housewife, on her husband's salary, and is looking forward to her operation and his return so that they may start making a life for themselves.

The patient is attractive and well developed. She dresses provocatively, and her body movements are extremely feminine. She is alert and witty, but somewhat vague and guarded when discussing her history. Her affect is appropriate. There is no evidence of thought disorder. There is no history of hallucinations, delusions, or previous psychiatric care. She admits to occasional depression, but denies suicidal ideation, and there is no history of suicide attempt. She is well oriented; her memory is intact. Proverb interpretation is appropriately abstract. The patient's judgment is fair, and her insight is good. She speaks freely about her desire to become a homemaker and a mother and hopes she will be able to get surgical treatment to be a "complete woman." She denies any sexual excitement from cross-dressing, denies orgastic experience through her male genitalia, and has experienced great relief from the testicular atrophy consequent to hormonal therapy. Her performance on the Minnesota Multi-Phasic Personality Inventory (MMPI) was essentially normal, although there is evidence on the femininity scale that points to her sexual confusion. She appeared to be somewhat defensive about taking the tests. Her performance on the Bender Motor Gestalt was essentially normal and ruled out organic disease. The Cornell Index Form N-2 displayed no evidence of psychiatric or psychosomatic disturbance. The patient is being seen in individual psychotherapy.

She was told that this interview would be part of a training session on transsexualism so that people in the Department of Psychiatry could learn more about it. She was also told that this session will have no bearing on her treatment, continuing evaluation, or the decision regarding her operation. She understands that coming here is entirely voluntary.

(The patient, whom we shall call Gloria, was escorted into the room. She wore women's clothing, was heavily made up, and quite attractive. She was introduced to Dr. Parzen,* who interviewed her before a group of approximately 100 staff members and residents. The following are selected excerpts from that interview.)

*Assistant Clinical Professor of Psychiatry, UCSD.

DR. PARZEN: Do you know why you are here this morning, Gloria?
Patient: To educate the staff.

DR. PARZEN: What does that mean?
Patient: To help the staff learn more about transsexuals. And to help transsexuals in their search for help.

DR. PARZEN: Where are you in your search now?
Patient: I'm waiting.

DR. PARZEN: What do you need yet?
Patient: The operations.

DR. PARZEN: What operations do you need?
Patient: I need to have the penis removed.

DR. PARZEN: Anything else?
Patient: Then after that the vagina needs to be formed.

DR. PARZEN: I see. Tell us what it feels like to be a girl now.
Patient: I finally feel as if I am happy, and if I get the operation then I'll really be happy.

DR. PARZEN: Tell us something about your feelings about the surgery if you're able to get it.
Patient: The most important thing is to have the penis removed, and after that, if possible, having a vagina created would be nice.

DR. PARZEN: Hmm. How do you feel about sex now? Is it mostly for the man?
Patient: No, I feel good about it too.

DR. PARZEN: How are you going to pay for this operation?
Patient: My husband and I have some money. He has an income.

DR. PARZEN: How much money are we talking about?
Patient: Probably around $2,000.

DR. PARZEN: Does your husband make that kind of money? And how does he feel about your having the operation?
Patient: He makes enough to pay for it, and he's in favor of my having the surgery.

DR. PARZEN: Why don't you tell me a little bit about how this all came about.
Patient: Well, since I was five years old I've always wanted to be a girl.

DR. PARZEN: Why did you want to be a girl then?
Patient: I don't know. I have no idea. I just did. I had a feeling I should have been a girl.

DR. PARZEN: How would that feeling have expressed itself? For example, to be a girl in this day and age means different things to different people. What did it mean to you at the age of five?
Patient: It's hard for me to explain. I wanted to be a girl—I knew what I wanted to be. But up to a certain point it didn't have too much importance because, well, there wasn't anything that could be done about it.

DR. PARZEN: How did you happen to learn that something could be done about it?
Patient: I heard my parents talking about Christine Jorgensen. When I heard about what happened with Christine Jorgensen I knew that that was what I wanted and that I would have the same thing done. I felt happy about that.

DR. PARZEN: Getting back to my earlier question about the meaning of your being a girl as you were growing up—let's say when you were ten years old—what did it mean then when you wanted to be a girl?
Patient: It didn't mean sex.

DR. PARZEN: It didn't mean sex. What did it mean? How was a girl different from a boy, other than physically?
Patient: It meant to be happy.

DR. PARZEN: What were the differences between boys and girls, say socially, that would make one want to be one rather than the other?
Patient: I don't know.

DR. PARZEN: Have you ever had any doubts about becoming a girl?
Patient: No.

DR. PARZEN: I understand that your marriage was quite recent.
Patient: Yes.

DR. PARZEN: How long did you know your husband before you married him?
Patient: I had known him for about three months. Two weeks after we were married he went overseas.

DR. PARZEN: I see. When your husband found out about the nature of the sexual issue with you, what was his reaction?

Patient: Surprise, of course. But we talked about it honestly with one another, and he decided he wanted to stay together and that he would support my getting the operation.

DR. PARZEN: I see. How do you feel when you put on make-up or do your hair? Is it a hassle? Does it make you feel good?
Patient: (smiling) It's just something I do.

DR. PARZEN: How do you feel if you don't fix yourself up? Do you feel real down?
Patient: No.

DR. PARZEN: Has there ever been a time in your life when you felt like you wanted to kill yourself?
Patient: No.

DR. PARZEN: Never felt depressed?
Patient: No.

DR. PARZEN: Ever had times when you might have heard voices or felt that people were out to get you?
Patient: No.

DR. PARZEN: Is there anything you want to ask me or any of the staff here?
Patient: No.

DR. PARZEN: (lightly) I guess you'd like to get out of here.
Patient: (smiles, shrugs, nods affirmatively) I guess so.

DR. PARZEN: Thank you for coming.
(The patient was escorted from the room.)

* * *

DR. PARZEN: My comments are going to deal with the psychiatric treatment of patients with transsexual problems, and in psychiatric treatment I include, with psychotherapy, endocrine therapy and surgical therapy, much in the way we might prescribe drugs or plastic surgery to help a patient deal with any sense of malformation that has affected his psychological functioning. One thing that transsexual patients have taught me is to differentiate primary pathologic from secondary pathologic states. Initially many such patients are depressed, or paranoid, or suicidal, and this is apparent on Rohrschach or Thematic Apperception Tests (TAT). As soon as a patient begins to get the message that you understand, that you empathize with him, then the depression, the paranoia, and other secondary pathologic changes diminish greatly if not vanish. It can take about a year to get under this superficial character structure and get a feel for such a patient as a person. The slip of the tongue in the presentation, when Dr. Millman said that Gloria was "the second of two daughters," probably tells us more than anything else about her, and about her mother's role, and so on.

In general I think one can look at transsexualism as a symptom complex that on the one hand is close to classical homosexualism and transvestism, and on the other hand becomes a very mysterious and difficult problem to understand. In this regard I feel that Dr. Stoller has defined a syndrome that includes pathological clinical manifestations and delineates a particular etiologic factor for one small group of patients. I believe that there is a large group of patients who are next to impossible to understand in genetic or dynamic terms. However, in working with these people one certainly has the feeling that they are *bona fide* transsexuals. The fantasy that every male transsexual has is, "If I were a girl, then I would be happy." I tried to get this fantasy from Gloria, but I couldn't get to it, which did not really surprise me. These patients become good actors and tend to be paranoid toward anyone who might push them to betray themselves in a way that might jeopardize their surgical treatment. Gloria had already established a personal relationship with Dr. Millman, and his feelings about her will ultimately determine what will happen to her.

Although there are patients from whom you can get a feeling for what their transsexualism is all about, I could not get such a feeling from this patient. Like many patients, she presents herself primarily as an external person. Her sexuality is based upon how things look. If she has a vagina she'll feel it, but otherwise it isn't important. She wants the penis removed because then she can appear more like a woman. How much of her life is externally oriented I could not determine. Certainly she is quite protective about herself at this point. She is awfully close to getting what she wants, and she isn't going to tell me anything that might interfere with that. She does not know my orientation, and she isn't crazy, and therefore isn't going to present material that might be interpreted wrongly from her point of view.

Transsexual patients classically tend to be very manipulative and very secretive. They tell you what they want you to know, and they have learned through much experience to read and to manipulate medical staff. Transsexuals tend to be hypersensitive in picking up clues in order to con-

struct a manipulative type of defense. In this regard they have some characteristics that are seen in some schizophrenics; they almost seem to know more about the interviewer than the interviewer knows about himself. Nevertheless, the manipulation, the character defense, is not the essence of their problem. Similarly the hallucination of the schizophrenic is not the essence of schizophrenia, nor is the suicide attempt of the depressive the essence of depression.

My impression is that the issues that lead to the clinical symptoms of transsexualism may occur at many points before the age of three. If they develop later in the age spectrum when symbol formation and words have begun to have communicative value, then it is easier for us to empathize and to understand the genetic origins and the dynamic struggle that is going on within the person. If the cause predates one year of age, when symbols do not have communicative value, then it is much harder to empathize with the dynamic and genetic issues involved; we are left to deal with the person as we see him now.

Today we saw a patient who has already come far along the pathway toward achieving her fantasy of becoming a woman. In speaking about this patient I say "her" unconsciously as well as consciously, even though I know that she is biologically a male. In some ways this indicates to me the probable right direction in which to go. That she has come this far toward her goal indicates that she is fairly well put together in terms of interpersonal relations and dealing with society. She can read the territory well, but, as I stated before, this ability *per se* is not the issue of her basic pathologic state. Her protectiveness in my brief interview with her was quite evident.

Generally, I feel that before one takes any irrevocable steps to fulfill a patient's fantasies one has to know a great deal about the patient. The professional bind that we are in stems from the fact that a lot of these patients become suicidal unless they have the surgical changes they seek, and some of them become suicidal after the operation, if not disturbed in other ways. I do not believe we have enough general clinical data as yet to have any predictive criteria. Ironically, we're so eager to get data that we don't work long enough or carefully enough with these patients before making decisions about what to do or not to do. One thing we do know is that psychotherapy alone rarely helps when the patient feels that we are only interfering.

Before I begin hormone therapy, I believe it is pragmatic to do a complete psychological workup, including the Rohrschach and TAT and an elaborate social history. It is valuable to interview the parents of the patient and any siblings, as well as people to whom the patient is relating at present. After this workup, which normally takes a number of months, is complete, if I still have the feeling that the patient would benefit from going through the transsexual procedures I begin hormonal therapy. After an appropriate interval, when there seem to be enough biological changes, then I have the patient go through a psychosocial change of identity. I repeat the Rohrschach and TAT at yearly intervals to pick up what is happening at a deeper psychic level that the patient cannot relate directly to me. It is very important to allow the patient to experience the new psychosocial identity for some time before going through with surgical changes. After a time the decision for operation is shared with the patient, and I let her know that there are no absolute rights or wrongs at this point. The decision is a significant responsibility, and I think it *has* to be shared. Both the therapist and the patient must recognize that it may fail, and both need to be ready to pick up the pieces.

Some people feel that you cannot change a transsexual after puberty, and this certainly presents a difficult ethical situation. I have one patient with whom I have worked for four years, and at this point he believes he wants to continue living as a male. The patient came to me very paranoid and depressed, and much of that has cleared. His superego has begun to ease up in therapy, and he has begun to allow himself narcissistic gratifications at various levels. He tends to be much less threatened by his own aggression, and his rage about his narcissistic frustrations has been considerable. He still gets depressed at times, but we are beginning to get a real dynamic feeling about the changes occurring within him. A lot more masculinity begins to appear—real masculinity, not stereotypic. Some people would say that inasmuch as my patient has given up his transsexual wishes he was never really a transsexual. I believe that this is splitting hairs and really does not face up to the issue of treating people who are suffering with this problem. The majority of patients who have not established adequate working relationships with therapists are

going to run off and get their surgical change someplace in an unstructured way that will be most unhelpful to them. My admonition is therefore to establish a relationship at the deepest possible layers of the patient's psyche so that she has someone she can turn to.

No matter which way this goes, Gloria is going to have trouble adjusting. A normal woman has trouble when she bears a child or adopts one; this new woman is going to have many more troubles. At this point she wants a baby because that is part of her image of being a woman. And yet I do not know whether she really wants a baby or whether this is just the image, just as she stated that she doesn't feel sexy if she doesn't have a vagina. Until you get under that image-oriented behavior I think you run certain risks with any patient. You owe it to the patient to establish your availability to step in and help along the way. You may even have to supply a woman to help this girl learn to be a better woman. Since this struggle has been going on she may not have had the opportunity to learn how to be the kind of woman she might be most comfortable being. As was pointed out in the history, she went through a brief extremely exhibitionistic phase and then seemed to settle into a more normal exhibitionistic pattern. In some ways this is similar to normal development; in some way she does not know what type of woman she wants to be.

Often transsexuals get together and find a beauty operator to help them make the transition. And of course many beauty operators tend to be exhibitionistic themselves. What would this woman be like if her coach were a sedate housewife? One of the feelings I have about Gloria is that she wants a home, and unless the man that she married is willing to supply an awful lot toward this goal for her, she is going to run into trouble. When she moves to the East and has lost many of the supports that she has here on the Coast, and her husband isn't around all the time because he is overseas or whatever, then reality will hit her fantasy, perhaps too late.

Hence I feel very strongly about a therapeutic alliance as a prerequisite for any drastic change for such a patient. Again, I would emphasize the ethical bind that one is in as a clinician treating such people rather than as an academician studying the problem. We know these patients can get their surgical operation, and we know they can get it without the appropriate psychological understanding that is necessary for an appropriate decision and an easier transition. The follow-up with these patients is of critical importance. Only after a number of years will we be able to look back at our original clinical data and have some predictive criteria to apply to the patients whom we are seeing then.

DR. GERNER:* There are references to cross-sexual behavior as old as Greek mythology, Hippocrates and the Roman poets, through the intervening centuries and in the anthropological literature. Most of the modern medical interest in people who desire sexual reassignment has arisen since the case of Christine Jorgensen was reported in 1953. One of the foremost contemporary authors on the subject is our guest today, Dr. Robert Stoller.[1] I'd like to mention a few others.

Dr. Harry Benjamin, in his book *The Transsexual Phenomenon,*[2] charts sex and gender role disorientation in males ranging from the pseudo transvestite, who has normal masculinity but occasionally gets a kick out of cross-dressing, to the true transsexual who has total psychosexual inversion and lives and works as a woman. He feels that psychotherapy is not useful in curing any of these except perhaps a fetishistic transvestite, but that supportive counseling is helpful to transsexuals. In his view only the true transsexuals of moderate or high intensity want and request conversion operations. For the patient who wavers between transsexualism and transvestism estrogen medication might be helpful in achieving a more emotionally balanced state, according to Dr. Benjamin.

Dr. John Money[3] has had extensive experience with transsexual patients at Johns Hopkins. His criteria for considering surgical sex conversion include a trial period of at least one year during which the patient takes hormones and lives as a member of the opposite sex, including holding a job. In a one- to 13-year follow up of 17 male patients, Money and his colleagues found all unequivocally sure they had done the right thing, even though there were postoperative difficulties. There were no cases of decline in occupational status among their patients. None acquired a new police record after surgical reassignment. Six patients had been arrested before the surgical

*Resident in Psychiatry, UCSD.

change; only two returned to former modes of illegal activity afterward. Psychiatric follow-up showed that none of the patients became psychotic, nor did any of them need psychiatric treatment for the first time after the operation. One needed psychotherapy before and afterward, however. Eight who received help before operation neither needed nor resumed therapy afterward. Money emphasizes that the operation cannot cure pre-existing depression, sociopathy, schizophrenia, or suicidal tendencies.

C. W. Socarides[4] has published a psychoanalytic study of an allegedly transsexual patient that runs counter to etiologic conceptions according to Benjamin or Stoller and Green. Socarides feels that the male transsexual is fleeing homosexuality, identifying with a powerful and hostile mother to neutralize his fear of her and achieve an infantile wish for intercourse with the father. However, the majority of transsexuals described in the literature are not characterized as fearful of their mothers —quite the contrary. Furthermore, Socarides's patient felt that he had a tumor between his legs; he attempted to emasculate himself; he had severe oral conflicts; in his infancy and early childhood he is reported as not able to bear being separated from his mother and to have been involved in great conflict with her about eating. There is said to be a delusional quality about his conviction that he was basically a person of the opposite sex.

Socarides's work, however, does suggest the possibility of viewing these patients along a continuum of people who have more or less thought disorder with cross-gender identity manifestations. Many people who meet the usual criteria for transsexualism have a bizarre quality about them and difficulty in focusing on present and past realities. Further, genetic difficulty or biochemical predisposition has not been ruled out absolutely, although hormonal, endocrinological, and neurological workups have found these patients to be within normal limits until they start taking hormones, which may be around age ten or twelve.

At UCLA Dr. Richard Green,[5] who with Dr. Stoller places great emphasis on behavior modification in addition to a symbiotic relationship with the mother as etiological in this condition, is treating youngsters in a long-term prospective study. These boys at age four or five are already very feminine in their behavior and gestures. In Dr. Green's experience the inordinately feminine boy usually comes to psychiatric attention first not because the parents are concerned about his effeminancy but because he is a behavioral problem at home, defying the routines in his desire to be feminine, or because on his entering school the authorities discerned a grossly abnormal behavior pattern and instructed the parents to have the child evaluated. The treatment strategy has been to develop an empathic relationship with the boy, act as an active role model, and intervene with the parents, teaching them how to be better role models and to encourage masculinity and discourage femininity as they are understood in our culture.

Sometimes legal problems can be as vexing to transsexuals as their medical or psychological problems. Most states have laws against cross-dressing or impersonating a person of the opposite sex. We don't know much about how the law affects transvestites or transsexuals unless they are caught, and then their fate depends a great deal on the judge and his interpretation of the law. Some district attorneys have been said to invoke a sixteenth century English law against surgical disfigurement to avoid military service as a threat to some physicians who attempt to treat transsexuals.[6] Some states routinely issue new birth certificates after reassignment operations; others do not. It would seem that a legal name change would not be as difficult. Problems arise from the fact that the terms *male* and *female* have never been defined by the courts in a manner that might apply to the patients in question.

Dr. Stoller:* Not everyone who asks for a sex-change operation has the same character structure, behavior, femininity, or etiologic factors. My ideas about the differential diagnosis of male transsexualism are linked to the search for the causes of those other conditions in which a person says, "I want to be changed into the opposite sex." The process begins with observation, even of such details as the style with which one walks into an interview, talks with you, and then walks out. It's in the subtleties of behavior that you can pick up clues essential for differential diagnosis.

Considering the differential, we should turn first to those who as a result of a biological factor wish to live permanently in the opposite sex—for example, those with Klinefelter's syndrome. In this condition (XXY) the extra X chromosome ap-

*Professor of Psychiatry, UCLA.

parently produces a diminution of total maleness. Such patients are sterile and usually have small male or hermaphroditic genitals. Frequently at puberty they develop breasts and some softening of muscular build and body contour. In a number of cases it has been reported that the man was unusually effeminate as a child or adolescent. Some are overtly homosexual. So the first step in the differential diagnosis of male transsexualism is to rule out the patients who have clear-cut biological correlates to their behavior. Next you have to consider a much larger and more controversial population of patients—those without biological defect.

The first group: *psychotics.* One of the commonest symptoms in the male psychotic is a gender complaint. Perhaps it would be invariable if you could question closely enough, but even on superficial inquiry a majority of males who are psychotic complain that their bodies are being influenced in such a way that their sex is changing. In other words, transsexual fantasies are typical in male schizophrenics. In a certain number of psychotic patients the condition is never diagnosed, or at least they are never put into a hospital for their thinking disorders. Some of the ones who are not grossly psychotic request sex-change procedures, and if they have enough money they can generally find someone who will perform the procedures. One of my patients, who felt that he should be a woman, was thrilled at the opportunity to dress up as a woman. He would *not* be sexually excited by this—an important differential point. He was happy to pose for me in a dress because he wanted people to see this happy woman displaying her lovely happy self. He made himself a wig for the occasion. While his appearance was bizarre, he had no insight about this, posing for photographs in strange and inappropriate postures. His idea of femaleness, as the pictures reveal, was different from women's. He finally did get operated upon, in the following manner. I hadn't seen him in years when I got a letter from him that went something like this: "Dear Dr. Stoller: How are you? I am fine. I am living in such and such a place. I pay rent of so much. Last night I went into the bathroom and I took my scalpel and thread and I then dissected, as I had read a medical book. . . . " And he described in this flat, calm fashion how he took his testes off and put them in a jar. Chances are that anybody who castrates himself is schizophrenic. Beware of operating on that large group of psychotic but not-too-psychotic patients with transsexual fantasies.

Second group: *transvestites.* I restrict the term *transvestite* to a person who puts on the clothes of the opposite sex because the clothes themselves create genital sexual excitement. Even when dressed in women's clothes these men do not usually impress you as being women. When a transvestite strikes a pose, there may be nothing in his posture that expresses femininity; rather it is a performance or imitation. In the photographs these people take of themselves you often get a strong sense that the subject *knows* something—such as, that he is not a woman. No effort has been made to disguise his maleness. He is doing this for fun, especially to get sexually excited. Invariably, a fetishistic male in female garb sits in my office as men do, with legs apart or otherwise unshyly and unseductively showing thigh, as if to announce there is still a penis. That's very different from the way someone sits who has an inner sense of femininity.

Transvestism, like any other perversion, is a piece of character structure invented in childhood to deal with an insoluble traumatic experience. The "solution" is lifelong, and has to be reapplied constantly. Although transvestites may gradually get to look more like transsexuals, pass more regularly, and eventually even live in society as women, they almost invariably have ambivalence about surgical change of sex organs and will turn back from it if permitted. The man who gets an erection from wearing women's clothes has that ambivalence, that flaw in his attempt to patch over an identity and make it whole.

On the other hand, the third group, *male transsexuals,* are the most feminine of males, and, what is more, they have *always* been. Some transvestites have learned to be feminine, but true transsexuals have *never* had masculine behavior. Their femininity starts as soon as gender behavior starts, somewhere around one year of age, and it is *spontaneous.* The child starts it, not the parent. The first time these kids had the freedom to choose, they chose feminine behavior, feminine clothes, feminine style. Femininity is also integral to them as adults; they don't have the capacity for masculine behavior. They suffer in school because, although dressed in boys' clothes, they cannot even

imitate boyishness. They are so often bullied that they attempt to change their sex or at least to pass by the time they're in their teens, powerfully driven to seek the operations. The ambivalence other patients express in delays or rationalization is not present in the transsexuals, who will change instantly if given the opportunity.

In snapshots of these children at age one, or two, or three it is clear that they did not start out masculine, as do transvestites or effeminate homosexuals. We can thank the mother, if thank is the word, for liking what she observed in her son enough to preserve it in the pictures we have studied. And indeed, it is the relationship between this mother and her son that represents the major etiologic aspect of male transsexualism as I see it.

Let me give you just the distillate of what we have learned about the typical mother of a male transsexual. She is chronically depressed and feels her life is worthless. As a child, having learned from her mother that being a female is a worthless state, she was unable to identify with her mother and turned to her father and his masculine interests, only to be abandoned by death, separation, divorce, or his attention to a younger sister. Then, in latency (age six or so until puberty) this mother-to-be of a transsexual behaved as if she were transsexual herself. She adopted exclusively masculine clothes, interests, and behavior. But on reaching puberty she was told by her biologic state, "You are female; you cannot escape it; you are—as your mother knew—worthless." She put on a feminine facade and married the first man who proposed, although she knew—sensed as soon as they met—that he was distant and empty.

And so a male child is born to this depressed woman and an empty, distant man. *If* the mother finds the child pleasing and *if* he is beautiful the mother and child experience from the beginning a lush mutuality, a blissful symbiosis; their bodies and psyches merge. Such a child has total freedom upon his mother's often nude body for too extended periods of time. There is almost no space between them. The baby is not a separate object but becomes as much a part of mother's body as she can manage. He is to have no identity except as a part of her femaleness and her femininity. There is nothing sexual or incestuous in this; this little boy feels no excitement toward his mother but rather feels as if he were she (identification). He is no Oedipus competing with his father, for his father *is* no competition. The father is absent and maligned by the mother; and, being absent, the father provides nothing for the boy to identify with.

So this family constellation is established and then maintained and reinforced, and by the time the child is four or five the die is cast. The symbiotic bond has somehow transmitted mother's femininity to the child, and he says, right from the start, "I am feminine." It is thus no surprise that when the time comes he asks to have his "distorted" body changed into its "proper" form. As a result, when you see these people you are seeing the real thing, a form of real femininity, not facade, imitation, or caricature. The danger for us as diagnosticians, therapists, and prognosticators is that other patients can, for shorter or longer periods of time, simulate this condition, and if all *those* people are called transsexuals, and if they are operated upon, there may be trouble.

Dr. Judd:* I see some parallels between this account and Jerome Kagan's model for the process of identity formation that might help us deal with the gap between the initiation of the symbiotic relationship and the accomplished phenomenon of a transsexual individual by the age of four or five. The four elements in Kagan's model of identification are (1) perception of one's similarity to a model, (2) sharing in the model's affective states, (3) realization that the model has access to options or privileges that the child wants, and (4) the actual acquisition of the attributes of the model. Here, the initial selection implies a mutual perception of similarities between the child and the mother. The extraordinary physical and psychological intimacy would provide shared affective experiences. The default of the absent, ineffectual father accords to the mother the power and privilege which the child might share were he like her. It only remains to become like her entirely.

Dr. Stoller: That is a very useful skeleton on which to hang data. There is one detail about which I want to say a few more words. At this point I don't think it's *all* identification, although I agree with your description of identification. Identification, I think, requires a psychic condition advanced enough that the child knows there's something out there to take in. We may find, however, that some of this early taking-in has a primitive biophysical basis—that some things can go directly from the mother's mental life to the

*Professor and Vice Chairman, Department of Psychiatry, UCSD.

child's relatively naked nervous system, which is not yet sophisticated enough to defend itself with psychological mechanisms. But that's speculation; right now it breaks my heart that we have no direct evidence about the first few years in these boys' lives because we don't see them until they are four or five. Still, we have some evidence that it started at birth. It's too bad, but we simply don't have the data to fill in that gap yet.

DR. MILLMAN: *Dr. Stoller, could you describe the differences in the ways the mothers of intersex patients who are not transsexuals dealt with them as children?*

DR. STOLLER: Allowing for some overlap, it would go something like this: The transvestite is someone who developed for at least a few years in a masculine manner. As a child he had a feeling of value about being a male and being masculine. He had what I call a male *core gender identity*—that is, the unquestioned belief that he belonged to the male sex and the desire to do so. And he wasn't going to give it up. Then some enraged, disappointed, envious, or traumatized woman punished that little boy for the masculinity he'd displayed. She put him into what *she* thought was a despicable state: feminine. She put girls' clothes on him. And when she did so, he knew that he had been humiliated. Then, as the years passed, he created the full-fledged perversion—a complicated scenario invented piece by piece out of daydreams to reverse the trauma and create a triumph. Now, "When the women's clothes are on me I don't lose my masculinity. Instead, I have an erection. I win: I can put on women's clothes and still be a male."

In the history of an effeminate homosexual (there are many kinds of homosexuality, and this description does not fit most) we often find a mother who was overpossessive, overprotective, and overgiving, but only when the little boy did what she wanted, only when he was unmanly—effeminate. She trained him as you'd train a seal; she wouldn't give him what he wanted unless he gave up the conscious display of the masculinity he was already developing. Effeminacy is mimicry; the effeminate homosexual is making fun of women.

In my theorizing I have oversimplified, of course. but I do believe that in the development of masculinity and femininity you usually get an adult behavior fitted to the parents' handling. Thus, since the process of feminization occurred atraumatically in the transsexual the femininity is natural-appearing. But for the male who was traumatically put into girls' clothes it's, "I'll put on girls' clothes, but I *won't* become feminine." For the effeminate homosexual it's, "O.K., I will act as you want, but secretly I will not give up who I really am."

DR. JAMES MORRISON:* I wonder about a biological, possibly genetic, mechanism. If these children are distributed evenly through a siblingship, perhaps there is a genetic factor. I would expect an environmental etiologic factor if they invariably were, say, the last born, or if there were no twins who were transsexual, or if there were relatively few cases of adopted transsexual children, with whom a mother would be less likely to experience such intense symbiosis. Are other family members, particularly the children of the sisters of the patients, ever found to be transsexual?

DR. STOLLER: I'll make my answer a step at a time. *One:* In the three families so far reported who had more than one male transsexual all of our criteria were met: the father was absent; the boys were beautiful; the mother was excessively close to the boys. *Two:* The only two reported cases of extreme gender identity disorder in identical twins support this thesis. In the male pair, the twin who was held intensively and excessively close is feminine; the other is masculine. In the female pair, one is feminine; the other was treated in the manner that I have described as causing female transsexualism (which is quite a different entity than male transsexualism), and she is masculine. *Three:* Position in the family has not proved determinant, only how much time was available for the symbiosis to flourish. In each of my cases the boy was the youngest child or there was time between his birth and that of the next sibling for the mother to concentrate herself upon him and do what she needed to do. *Four:* Adopted transsexuals are apparently extremely rare. In the one case I know of involving an adopted child the baby was adopted at birth. *Five:* The sisters of transsexual boys whom we see are neurotic—but feminine; none is transsexual. We don't have data on them as adults; it's too soon.

DR. MANDELL: It is obvious that Dr. Stoller knows this behaviorally deviant subculture as few do, but I would like you also to appreciate that he

*Assistant Professor of Psychiatry, UCSD.

brings us these insights out of long years of the most painstaking, rigorous scientific research. He is one of the few people in the world who are using classical psychoanalytic methods in research —the prolonged, patient, free associative, intimate, detailed observation and documentation of internal human phenomena for the purposes of discovery.

To deal with a person who has this conviction that "he" is really a woman in a man's body, we must learn to empathize with this form of human behavior, and to do this effectively we have to be aware of our own hang-ups, our own psychosexual defenses. In a sense it involves getting in touch with the opposite sex that is in every one of us, and that can be pretty threatening. Essentially what these people are struggling with is a problem of identity—an overwhelming need to find an identity with which they can be comfortable, into which they can relax. And when we go in to try to help them we have to do it with a feather, gently. We are not public prosecutors—we don't enforce any law that says the way these people behave is illegal—we're physicians, and the first rule, always, is to do no harm!

REFERENCES

1. Stoller RW: Sex and Gender. New York, Science House, 1968
2. Benjamin H: The Transsexual Phenomenon. New York, Julian Press, 1966
3. Money J: Preferatory remarks on outcome of sex reassignment in 24 cases of transsexualism. Arch Sexual Behavior 1:163, 1971
4. Socarides CW: Psychoanalytic study of the desire for sexual transformation—Transsexualism, the plaster of Paris man. Int J Psychoanalysis 51:341, 1970
5. Green R: Diagnosis and treatment of gender identity disorders during childhood. Arch Sexual Behavior 1:167, 1971
6. Sherwin RV: The legal problems of transvestism. Am J Psychother 8:243, 1954

EDITORIAL COMMENT

Refer to: Fisk NM: Gender dysphoria syndrome: The conceptualization that liberalizes indications for total gender reorientation and implies a broadly based multi-dimensional rehabilitative regimen—Editorial comment on male transsexualism. West J Med 120:386-391, May 1974

Gender Dysphoria Syndrome—The Conceptualization that Liberalizes Indications for Total Gender Reorientation and Implies a Broadly Based Multi-Dimensional Rehabilitative Regimen

NORMAN M. FISK, MD, *Palo Alto*

RECENTLY THERE HAS BEEN an ever increasing interest or perhaps even a preoccupation in both the professional and lay sectors of the populace in a relatively small and select group of people who have been variously labeled or mislabeled as transsexuals. Professional interest is understandable based upon the fact that the complexities surrounding gender and all it implies are intriguing and challenging. Lay preoccupation, as demonstrated by a plethora of newspaper and magazine articles, television and radio talk shows, and books written for the laity by both professionals and patient alike, is superficially understandable given the exotic and often bizarre qualities implicit and explicit in this subject.[1-5] I would not discount a certain element of quasi-prurient interest or titillation that is understandable in professional and laymen alike.

Currently, it is most fadistic in certain intellectual and creative elite subgroups to demonstrate a fascination with cross-gender behavior and particularly in those who pursue this behavior. Beyond this, however, there likely dwells within us all a primal curiosity concerning the hows and whys of the particular gender orientation we embrace. Throughout recorded history as well as in multiple culturally determined legends and myths, there is ample evidence that cross-gender behavior has long been a fact of human existence.[6]

The term *transsexual* was coined by Dr. Harry

Reprint requests to: N. M. Fisk, MD, 900 Welch Road, Palo Alto, CA 94394.

Benjamin, an esteemed pioneer in the field of gender disorders.[7] Dr. Benjamin has written extensively about gender disorders and has had a vast and intensive clinical experience spanning many decades. The term (or diagnostic label) *transsexual* as applied to the male and female has seemingly served well to communicate salient differences existing between persons who have certain distinctive and aberrant emotional and behavioristic symptoms. As originally intended, the term *transsexual* was to specifically identify a person who was not to be confused with a homosexual or a transvestite. Many authorities on gender aberrations have considered it extremely significant to accurately define a differential diagnosis between the aforementioned conditions as well as all types of biologic intersex. While I would agree that the elucidation of biologic intersex is an essential prerequisite to the treatment of gender disorders, I feel rather strongly (given the experience of the Stanford University gender dysphoria program) that the differential diagnosis aimed at clearly identifying a subgroup of patients termed transsexuals is in many instances a rather non-productive effort. Beyond this, differential diagnosis does not significantly bear upon the success or failure of ensuing treatment.[8]

In a classical sense the male transsexual was a person who demonstrated lifelong behavior that was effeminate or imitative of the opposite sex, had a deep and abiding conviction that he was indeed a member of the female sex or gender, and that this non-psychotic conviction led him on an incessant search for medical and surgical transformation into the sex to which he felt he legitimately belonged. Further it was felt that transsexuals found their own genitalia repugnant or repulsive and also considered any interest (in his own genitalia) on the part of members of either the same or the opposite gender unpleasant. Such a person was often therefore described as rather asexual. Also it was strongly emphasized that the cross-dressing phenomenon should not and indeed must not carry with it any erotic connotation, as this would point directly toward the diagnosis of male transvestitism. As an addendum, I might add that many authorities felt the effeminate homosexual would very seldom pursue an intense search for surgical and medical gender reorientation, would derive reasonable sexual gratification from his own genitalia and if he would cross-dress at all in the fashion of "dragging" this would be done merely to enhance his attractiveness to other homosexuals. The medical literature stressed, in keeping with the revered concept of *primum non nocere,* that it was essential to clearly differentiate the classical transsexual from all other forms of gender deviation because if this were not done, gender reorientation with accompanying surgical sex conversion would not be the indicated treatment and could potentially prove to be harmful.

In 1968, armed with this knowledge and the insights gained by visiting various active gender reorientation programs throughout this country, staff members of Stanford University Medical Center embarked upon a clinical research project that ostensibly would answer the question of whether or not surgical sex conversion as part of gender reorientation was a beneficial means of treatment. Viewed in retrospect, this was a somewhat naive effort, for the research design did not provide a control group nor could it feasibly be expected to do so. More specifically, a decision was made to carefully screen applicants for surgical sex conversion and accept those who seemingly were good or ideal candidates and pursue what had heretofore been a rather arduous project of intensive and extensive long term follow-up. The fact that a matched control group not receiving surgical conversion would not exist obviously obscures the answer to the question regarding the benefit or lack thereof of surgical sex conversion. Our data, however, do allow us to answer an equally if not more pressing question and that is: Does surgical sex conversion harm a rather diverse group of patients who we feel are better identified as having gender dysphoria syndrome? The dictionary definition of gender as applied to its non-grammatical meaning, merely states *sex.* It is well known to students of biology and behavioral science that gender is a complex and convoluted compilation of a number of biological, psychological and psychosocial factors. Chromosomal make-up, sex of assignment and rearing, external and internal genital morphology, pre-natal and post-natal endocrinologic factors, as well as behavior, are all seemingly interrelated within the concept of the gender. A dictionary definition of dysphoria includes dissatisfaction, anxiety, restlessness and discomfort.[9]

Within the first two to three years of our investigation, it became apparent that when non-fabricated or, more precisely, honest and candid psy-

chobiographies were obtained from our patient population, there was indeed a great deal of diversity and deviance from what had been defined as the symptoms of "classical transsexualism." Moreover, the overtly present common denominator was the high level of dysphoria concerning the individual's gender of assignment or rearing. It became readily apparent that people presenting with gender problems actually made up a spectrum of gender disorders ranging from the mildest to the most severe forms of this affliction.

I readily agree that classical transsexualism as best described by Dr. Benjamin represents the most extreme form of gender dysphoria; and further, there is almost certainly operational within these persons a significant biologic, organic or somatic component to their problem. There are both ample and significant data available that in many sub-human species, gender behavior as well as gender determined endocrinologic function can be irrevocably changed by experimental manipulation of intrauterine and post-natal steroid sex hormones, particularly as related to the brain and hypothalamic areas.[10-15] There exists strongly suggestive evidence that in humans, too, hormonal aberrations bear a relationship to deviations of gender-associated behavior.[16,17] Recently, there have also appeared highly provocative reports of abnormalities in androgen metabolism in male homosexuals.[18-22]

In a quasi-humorous, but nevertheless, pertinent fashion, I can now easily formulate a conceptualization of gender disorders which would even include what could be termed in a Freudian paradigm "the psychopathology of everyday life," and that is that the mildest form of gender dysphoria might well be demonstrated by an apparently normal, well-adapted male who in all facets of his behavior, including his choice of sexual object, is overtly masculine. However, he chooses to participate for one to two weeks a year in his civic club's annual skit. His choice of participation is to cross-dress as a can-can girl or a member of a chorus line attired in female garb, and perform a dance routine. This is usually greeted by a fair degree of hilarity on the part of the viewing audience. I do not imply that this person has a form of behavior deviant enough or so significantly abnormal as to be so labeled or as to require treatment. I do wish to emphasize that not all men would derive pleasure or excitement or enjoyment from this particular type of activity; and, given that fact, I would once again reiterate that this would serve as an example of "psychopathology of everyday life" *vis à vis* gender dysphoria syndrome.

Encompassed in a spectrum of gender disorders would be effeminate homosexuality or hyper-masculine homosexuality in the female, male and female transvestitism, a fascinating subgroup of patients who could be termed inadequate passive-dependent personalities with a mild to moderate transvestic fetish and a group of overtly sociopathic persons who merely seek gender reorientation or sex conversion operations as a means of becoming a "professional" transsexual and thereby to gain fame, notoriety and wealth. Finally, many psychotic patients have a severe type of gender confusion. Twenty percent of all patients contacting our program are overtly psychotic and are of course referred for or given appropriate psychiatric treatment.

The concept of gender dysphoria syndrome grew out of clinical necessity very much in an organic, naturalistic fashion.[23] This occurred because virtually all patients who initially presented for screening provided us with a totally pat psychobiography which seemed almost to be well rehearsed or prepared, particularly in the salients pertaining to differential diagnoses. It would be accurate to say that of the initial 30 to 40 non-psychotic patients screened, all presented as virtual textbook cases of classical transsexualism. Remembering the old medical saw that "the last time one sees a textbook case is when one closes the textbook," it was apparent that this group of patients were so intent upon obtaining sex conversion operations that they had availed themselves of the germane literature and had successfully prepared themselves to pass initial screening. In some instances they had rehearsed friends, spouses and family members in a similar fashion. Not all of them did this in a necessarily conscious, overt or sociopathic fashion. Many, in a subtly unconscious way, had retrospectively examined their life history and had amended certain key areas so that to themselves they did indeed represent the entity of classical transsexualism. I feel that many of these patients were in full flight from either effeminate homosexuality or transvestitism and were rushing to embrace the diagnosis of transsexualism for many valid reasons. Notwith-

standing our currently more liberal or permissive society, it is certainly much more acceptable and non-socially stigmatizing to have a legitimate medical illness than it is to suffer from a supposed moral perversion, sexual deviation or fetish. The pressures exerted by society at large as well as by various significant loved ones in the patient's life were sufficient in many instances to cause the patient to take on all the symptoms of classical transsexualism in order to obtain surgical sex conversion.

By employing the diagnostic term *gender dysphoria syndrome,* our indications for surgical sex conversion therapy have been broadened. Patients now clearly understand that had they been interviewed five or ten or twenty years ago, they would have been diagnosed as not being classical transsexuals. These patients are informed that a diagnosis of transsexualism is not in our view the only valid criterion for deciding who receives surgical sex conversion. Moreover, we practice the rather pragmatic dictum that nothing succeeds quite like success and therefore our criteria for surgical sex reassignment or conversion are more phenomenologically oriented. We are far more interested in the patient's status here and now and in the recent past, than we are in establishing a differential diagnosis. We avidly seek to determine how well or how badly a particular person has been coping and will cope with life in his gender of choice. Oftentimes patients have been living totally in their gender of choice along with the exogenous administration of the appropriate sex hormones for many years before they come to our facility. In the instances in which this is not true, then a mandatory period of trial cross-living on a 24 hours a day basis while receiving exogenous hormone treatment is requested for a minimum of 12 to 18 months, following which a thorough reevaluation is performed.

Factors such as physical passability, vocational skills, overall psychic and emotional stability, past and present ego strengths, familial support, appreciation of core gender principles, absence of significant sociopathy, absence of phychotic symptoms and multiple or intensive neurotic symptoms (as manifested by impulsivity, poor judgment, deviousness, narcissism, manipulativeness, masochism, exhibitionism and low self-esteem) are all factors that are heavily weighed in the overall team decision as to acceptability for sex conversion. Obviously, by liberalizing the indications for sex conversion through conceptualizing patients as having gender dysphoria, we also are committed to provide a program for patients encompassing many factors related to a total overall rehabilitative experience. These include vocational counseling and guidance, psychological and psychiatric supportive therapy, grooming clinics where role-appropriate behaviors are taught, explained and practiced, legal assistance, and, probably of most benefit, an opportunity is afforded to meet and interact with other patients who have successfully negotiated gender reorientation or who are in various phases of reorientation. This program employs some former patients as counselors to persons with gender disorders. Whenever possible, family members are included in the appropriate phase of gender reorientation.

To leave this subject without strongly emphasizing an all too often neglected point would be inexcusable. I refer specifically to the adequacy of the surgical sex conversion procedure itself. It is obviously an impossible task to evaluate the success or lack thereof of surgical sex conversion if the operation has not been performed in a manner that will allow the patient to function sexually with ease, enjoyment and assurance of a reasonable chance for success. All too often we see rather pathetic examples of patients who have acted impulsively or injudiciously and have sought surgical sex conversion by means which they consider to be most expedient. It is well known that this particular group of patients are extremely vulnerable to easy exploitation by charlatans and quacks. The tragic results are seen in persons who have had inadequate surgical operations and are not able to perform sexually either with ease or, in some instances, at all. These people represent a rather desperate and intensely frustrated and depressed group who require, where possible, expert surgical revision of procedures previously poorly done. Ofttimes the flagrant exploitation of these patients also includes participation in illicit markets for sex steroids, silicone injections and rather poorly performed ancillary surgical cosmetic procedures. It is for these reasons that it is critically important for reputable and responsible physicians to recognize the "medical legitimacy" of gender disorders and, where possible, to attempt either to successfully treat such patients or to refer them to those who can.

Unfortunately, both in the past and even now many physicians find it extremely difficult to separate their professional diagnostic and treatment skills from their own particular value system, which in some instances is highly tinged with moralism and judgmentalism. I have had the unpleasant experience of hearing a number of colleagues voice the opinion that gender reorientation with surgical sex conversion is an "immoral procedure" and in one particular instance have seen in print the statement that surgical sex conversion is "tantamount to medical malpractice." It is inconceivable to me how any valid attempt at the alleviation of human suffering and despair can be immoral. I certainly do not unequivocally believe that gender reorientation with surgical sex conversion will always remain the treatment of choice for persons with significant gender problems. However, it is rather well known and accepted that any mode of psychotherapy rather uniformly fails to alleviate symptoms. Therefore, in the present state of our knowledge there is seemingly ample evidence to indicate that gender reorientation with surgical sex conversion is a form of treatment that affords certain selected patients an opportunity to live a more joyful and fulfilling life.

The documentation of the feasibility or advisability of sex conversion is based upon our rather exhaustive five-year follow-ups that clearly indicate, in every instance of surgical sex conversion, that patients expressed the opinion that they were subjectively far happier than they had been before.[8] There exists additional evidence to further validate the point that for all groups (except for the gender dysphoria syndrome sub-diagnosis *transvestitism*) there was statistically significant improvement in social adjustment, psychologic adjustment, economic achievement and, for all groups, including transvestites, a highly significant improvement in sexual adjustment.[8] Lest this be viewed as a totally glowing report, I would add that our findings are congruent with other follow-up studies which indicate that gender reorientation does not significantly alter the fundamental characterologic structure of the individual patient. For this reason we more firmly than ever believe that the phenomenological selection of patients is far more appropriate than selection based upon differential diagnosis. Dr. Donald Laub, who heads the surgical team that performs the reconstructive operations, feels very strongly that the flexible, yet at once somewhat rigid, behavioristic requirements for acceptability into our program represent a very unique and distinctive form of behavioristic psychotherapy. Many patients who are initially denied surgical sex conversion are placed on a "hold" status to be re-evaluated again later. Implicit in this delay is the message that they should improve the overall stability of their life-style. For many patients this involves a waiting period of two to four years, and during this period pronounced changes in at least superficial behavior are observed. If one adheres to a doctrine of thought that believes a person eventually becomes what he or she seems to be, then Dr. Laub's supposition would indeed seem to be correct.

As a concluding thought, it should be stated that the surgical procedures involved for both males and females suffering from gender dysphoria syndrome are quite major and complex, and there is a significant rate of surgical complications. To date there have been no deaths reported in our series of 90 patients operated upon. Similarly, there have been no major psychiatric casualties in the form of psychotic decompensation, severe clinical depression or suicidal behavior. We are bringing to bear upon the problem of gender dysphoria the resources of a rather vast and well-equipped medical center, and this point must be strongly emphasized. In many instances these patients are very troubled persons who are extremely difficult to deal with; and the difficulties involve their families, loved ones and even their physicians, and they present challenging and oftentimes vexing problems. We would stress that physicians contemplating the thorough treatment of patients with gender dysphoria syndrome have in their armamentarium of therapies sufficient and significant ancillary and supportive paramedical facilities. These can be of immense help and can significantly ameliorate or prevent either patient or physician dissatisfaction and frustration.

There remain many unanswered questions concerning etiology, incidence, epidemiologic factors and treatment in regard to this most fascinating and troubled group of patients who all too often pose a problem that might be best expressed as "Help us, if you dare."

REFERENCES

1. Berg RH: The transsexuals—Male or female? Look pp 28-31, Jan 27, 1970

2. Anonymous: My daughter changed sex. Good Housekeeping pp 87, 152-158, May 1973

3. Anonymous: Transsexual. California Girl, pp 14, 62, Jun 1973

4. Transsexualism Article. Penthouse, Jan 1974

5. Prisoners of sex. Time Magazine p 65, Jan 21, 1974

6. Green R. Money J: Transsexualism and Sex Reassignment. Baltimore, The Johns Hopkins Press, 1969

7. Benjamin H: The Transsexual Phenomenon. New York, The Julian Press, Inc., 1966

8. Laub D: A rehabilitation for gender dysphoria syndrome by surgical sex change. J Plastic and Reconstructive Surg, Apr 1974

9. Random House Dictionary

10. Baker HJ, Stoller RJ: Can a biological force contribute to gender identity? Am J Psychiat 124:1653-1658, Jun 1968

11. Harris GW: Sex hormones, brain development, and brain function. Endocrinology 75:627-648, 1964

12. Young WC, Goy RW, Phoenix CH: Hormones and sexual behavior. Broad relationships exist between the gonadal hormones and behavior. Science 113:212-218, 1964

13. Davidson JM: Activation of the male rat's sexual behavior by intracerebral implantation of androgen. Endocrinology 59:583-594, 1966

14. Harris GW, Michael RP: The activation of sexual behaviour by hypothalamic implants of estrogen. J Physiol 171:275-301, 1964

15. Harris GW, Levine S: Sexual differentiation of the brain and its experimental control. J Physiol 181:379-400, 1965

16. Yalom ED, Green R, Fisk N: Prenatal exposure to female hormones. Arch Gen Psychiatry 28:554-561, Apr 1973

17. Ehrhardt A, Money J: Progestin-induced hermaphroditism: I.Q. and psychosexual identity in a study of ten girls. J Sex Research 3:83-100, 1967

18. Kolodny RC, Jacobs LS, Masters WH, et al: Plasma gonadotrophins and prolactins in male homosexuals. Lancet 2:18-20, Jul 1972

19. Margolese MS: Homosexuality—A new endocrine correlate. Hormones and Behavior 1:151-155, 1970

20. Loraine JA, Ismail AAA, Adamopoulos DA, et al: Endocrine function in male and female homosexuals. Br Med J 4: 406-408, 1970

21. Kolodny RC, Masters WH, Hendryx J, et al: Plasma testosterone and semen analysis in male homosexuals. N Engl J Med 285:1170-1174, Nov 1971

22. Loraine JA, Adamopoulos DA, Kirkham KE, et al: Patterns of hormone excretion in male and female homosexuals. Nature 234:552-555, Dec 1971

23. Fisk N: *In* Gandy P, Laub D (Eds): Proceedings of the Interdisciplinary Symposium on Gender Dysphoria Syndrome. Stanford, Stanford University Press. In press

HARD TO FIND ANTIPARASITIC DRUGS*

Drugs Available from the Parasitic Disease Drug Service

CENTER FOR DISEASE CONTROL
ATLANTA, GA. 30333
Weekdays (8 am—5 pm) (404) 633-3311 Ext. 3677
All other times (404) 633-2176

DRUG	PATHOGEN
Pentamidine Isethionate (Lomidine)	*Pneumocystis carinii* *Trypanosoma gambiense*
Niclosamide (Yomesan)	*Taenia saginata* *Hymenolepis nana* *Diphyllobothrium latum* *Dipylidium caninum (man)*
Sodium antimony gluconate (Pentostam)	*Leishmania species* *visceral (Kala-azar)* *cutaneous* *mucocutaneous (espundia)*
Melarsoprol (mel B)	*Trypanosoma gambiense* *Trypanosoma rhodesiense*
Suramin (Antrypol)	*Trypanosoma rhodesiense* *Onchocerca species*
Dehydroemetine	*Entamoeba histolytica hepatic abscess*
Sodium antimony dimercaptosuccinate (Astiban)	*Schistosoma mansoni* *Schistosoma hematobium*
Niridazole (Ambilhar)	*Schistosoma hematobium* *Dracunculus medinensis*
Bayer 2502	*Trypanosoma cruzi*
Bithionol, N.F.	*Paragonimus westermani*
Parenteral chloroquine	*Plasmodium falciparum*
Parenteral quinine	*Plasmodium falciparum*

*These drugs are used commonly in countries where such pathogens are endemic. With the exception of parenteral chloroquine and quinine, the drugs are not licensed for use in the U.S., however, they are approved for use here by the Food and Drug Administration (FDA). The drugs are available from the Center for Disease Control (CDC), but, because of their "approved only" status they are classed as investigational. The CDC, acting as "investigator," makes the drugs available to physicians provided that the investigation of the new drug protocol (IND) approved by the FDA is complied with and the completed IND is filed with CDC.

Information prepared by: Infectious Disease Section, California State Department of Health. October, 1973.

Refer to: The problem of diagnosis and classification of chronic hepatitis—Medical Staff Conference, University of California, San Francisco. West J Med 120:392-399, May 1974

The Problem of Diagnosis and Classification of Chronic Hepatitis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *This morning the Medical Grand Rounds will be devoted to a consideration of important problems in liver disease. The first patient to be presented will be summarized by Dr. Daniel Von Hoff.*

DR. VON HOFF:† The patient is an 18-year-old woman who noticed the onset of ankle edema, jaundice and dermatitis in February, 1970. She denied exposure to needles, drugs or hepatitis. In July, 1970, liver biopsy at the University of California showed chronic active hepatitis with piecemeal necrosis. Past medical history included diabetes mellitus diagnosed at age 12, treated with chlorpropamide (Diabinese®), and mild hypothyroidism with thyromegaly diagnosed at age 13. Laboratory data included a positive antinuclear antibody (ANA). She was treated with 60 mg of prednisone per day. She remained relatively asymptomatic, but continued abnormal liver function tests led to addition of azathioprine (Imuran®) in October, 1970 (25 to 75 mg per day). In June, 1971 liver biopsy showed nonspecific portal inflammation. ANA, hepatitis associated antigen (HAA) and lupus erythematosus (LE) preparations at that time were negative. On physical examination in January, 1973 blood pressure was 130/100 mm of mercury and the pulse rate 72. There were no cutaneous manifestations of liver disease. Hemoglobin was 11.2 grams per 100 ml, hematocrit 33.6 percent, platelets 256,000 per cu mm, leukocytes 7,400 per cu mm with a normal differential, sedimentation rate 34 mm in one hour, prothrombin time 12.6 seconds, serum glutamic oxaloacetic transaminase (SGOT) 50 international units per liter (IU/L), alkaline phosphatase 91 IU/L, and tetraiodothyronine low at 3 micrograms per 100 ml. Liver biopsy showed piecemeal necrosis and early cirrhosis, with improvement compared with previous biopsies. Imuran® was discontinued and prednisone tapered to 20 mg every other day. The patient is now asymptomatic without evidence of organomegaly. A recent SGOT determination was 70 IU/L, alkaline phosphatase was normal and bilirubin 1.2 mg per 100 ml.

DR. SMITH: *Thank you very much. This patient is being presented as a background for the discussion of the problem, the diagnosis and the classification of chronic hepatitis. We would like to call*

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†Daniel Von Hoff, MD, Intern in Medicine.

on Dr. Martin Brotman to open the discussion concerning this patient and more generally concerning this very important and frequent problem in medicine. Dr. Brotman is a member of our clinical faculty and is a frequent and excellent participant in our teaching program.

DR. BROTMAN:* The term *chronic hepatitis* is nonspecific and has led to a great deal of semantic confusion in the literature. This term may be applied to a variety of liver diseases which are long-standing and on histological study show inflammatory changes. I would like to focus on a practical and often confusing group of clinical problems—the classification, differential diagnosis and management of acute viral hepatitis (AVH), benign persistent hepatitis (BPH) and chronic active liver disease (CALD). The goal of this discussion is to determine how one identifies the patients with each, which of them require treatment, and how long to treat. Dr. Montgomery will discuss the histology of these entities, as the liver biopsy is the single most important diagnostic tool for their recognition.

This discussion will therefore emphasize: (1) the significant differences between the natural histories of virus A hepatitis (alias infectious MS-1, Type A, Australia antigen-negative, hepatitis associated antigen negative, HAA (−), Hepatitis B antigen-negative, HBAg (−), short incubation) and Virus B hepatitis (alias serum MS-2, Type B, HAA (+), hepatitis B antigen-positive, HBAg (+), long incubation); (2) the semantic confusion in the labelling, clinical presentation, biochemical and immunochemical features, and histology of "chronic active liver disease"; and (3) the differentiation of these life-threatening hepatic inflammatory diseases from the much less ominous "benign persistent hepatitis."

Acute Viral Hepatitis

A question often posed is, "When does one start to worry about chronic hepatitis in a patient with acute viral hepatitis?" Table 1 lists the appropriate "warning signals."

Chart 1, a composite graph from a number of publications,[1,2] demonstrates the natural history of HBAg-negative and HBAg-positive viral hepatitis following a controlled exposure. HBAg-negative hepatitis shows an average incubation period of 32 days and an average duration of clinical disease of 21 days. This form of hepatitis rarely leads to chronic liver disease. HBAg-positive hepatitis shows an average incubation period of 65 days before development of the clinical disease. The average duration of clinical disease is seven weeks. It is important to recognize that with HBAg-positive hepatitis of this type the prognosis may be excellent despite the prolonged clinical course. For HBAg-positive hepatitis the average duration of the clinical disease, be it clinical or biochemical abnormality, is significantly longer than for HBAg-negative hepatitis. We are often asked to see patients with hepatitis in consultation for liver biopsy because the SGOT is still elevated and they still have malaise and jaundice four to six weeks after the onset of their illness. This is not at all atypical for uncomplicated, HBAg-positive hepatitis. The important feature is that virtually all cases should have resolved within four months of the diagnosis of the disease. This is a useful rule of thumb—with a history of acute viral hepatitis the disease should resolve clinically and biochemically by four months. If it does not, liver biopsy should be considered.

Chart 1 also demonstrates the behavior of the

TABLE 1.—*"Warning Signals" in Acute Viral Hepatitis (AVH)*

- Persistence of clinical or biochemical disease, or HBAg, beyond four months
- Presence of physical "stigmata" of chronic or aggressive liver disease
- Presence of biochemical "stigmata" of chronic or aggressive liver disease

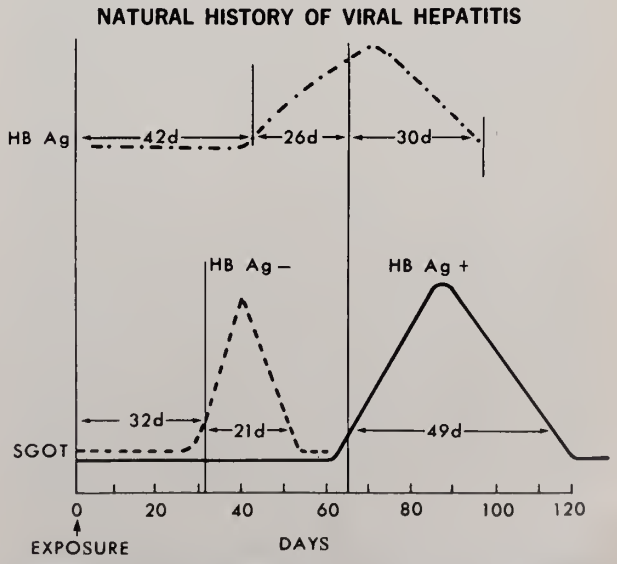


Chart 1.—Natural history of acute viral hepatitis. Ag^-, type A hepatitis; Ag^+, type B hepatitis.

*Martin Brotman, MD, Assistant Clinical Professor of Medicine.

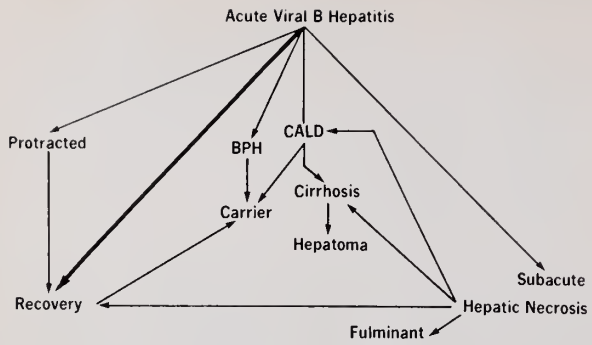


Chart 2.—Sequelae of acute viral B hepatitis. CALD, chronic active liver disease; BPH, benign persistent hepatitis.

hepatitis B antigen (HBAg). Following exposure, there is an average period of six weeks before the antigen appears in the blood stream.[3] Note that the antigen appears in the blood an average of four weeks before the development of clinical disease and remains demonstrable in the blood for a variable period, averaging about 30 days, after the development of clinical disease. Some patients will lose the antigen in two to three days. Hence it becomes important to search for the antigen early in acute hepatitis. Again, we can apply the rule of thumb of four months. Several studies have shown that if a patient who is HBAg-positive does not lose the antigen by four months he is likely to become a lifelong carrier. The younger the patient at the time antigen is detected, the more likely he is to retain the antigen. A significant proportion of chronic carriers of the HBAg antigen have an associated histological abnormality of the liver. The important question that arises is whether the liver abnormality is a benign one requiring no treatment (BPH), or an aggressive one requiring treatment (CALD).

In addition to persistently detectable HBAg, there are other diagnostic clues to chronicity in patients with apparent acute viral hepatitis.[4] Chronic active liver disease may mimic acute viral hepatitis. The patient may present with a "typical" prodrome and a "typical" massive rise of transaminase, yet already have chronic active liver disease. This patient is identified by recognition of the stigmata of chronic liver disease. If a patient appears clinically to have acute viral hepatitis, yet has such stigmata as ascites, edema, splenomegaly, spider nevi or liver palms, then liver biopsy is indicated promptly rather than after waiting for the four-month resolution discussed above.

TABLE 2.—*Subacute Hepatic Necrosis (SHN)—Characteristics*

- Viral B hepatitis
- Patients older than age 40
- Prolonged prodrome and course
- Bilirubin >15 mg per 100 ml, prothrombin <60 percent and albumin <3 grams per 100 ml
- Ascites, edema or encephalopathy

TABLE 3.—*Benign Persistent Hepatitis—Definition*

1. *Benign*
   Transaminase mostly, symptoms minor
   Not progressive
   No cirrhosis or portal hypertension
2. *Persistent*
   At least six months
   Persistent or fluctuant, indefinitely
3. *Hepatitis*
   Portal and focal inflammation

The third warning signal is hyperglobulinemia. Persistent elevation of serum globulin in apparently "acute" viral hepatitis suggests chronicity and again would lead to consideration of liver biopsy without waiting for four months.

Hence, to the question, "When does one start to worry about chronic hepatitis in a patient with acute viral hepatitis?" we can answer, "When the clinical and biochemical illness persists beyond four months, when the HBAg persists beyond four months, if there are stigmata of chronic liver disease at the time of diagnosis or during the follow up period, or if hyperglobulinemia is observed."

Chart 2 summarizes the possible sequelae of an episode of acute Viral B hepatitis. As was discussed previously, most patients will recover completely, some after a protracted course of several months.

Subacute Hepatic Necrosis

Before discussing the important differential diagnosis of BPH and CALD, I would like to review the entity of subacute hepatic necrosis (SHN). There has been some confusion about the diagnosis and classification of this entity because it crosses the line between acute viral hepatitis and chronic aggressive liver disease.[5] Although SHN clinically presents as an acute hepatitis, it is an aggressive lesion and must be treated with glucocorticosteroids. Table 2 presents the clinical features of SHN: Usually, but not always, HBAg-positive viral hepatitis; usually, but not always, an older age group, older than 40; usually a prolonged prodrome (more than the couple of weeks

TABLE 4.—*Chronic Active Liver Disease (CALD)—Definition*

1. *Chronicity*
   Persistent or fluctuant, progressive
   Longer than ten weeks
   Most die in three years, 95 percent in ten years
2. *Activity*
   High transaminase, hyperglobulinemia
   Hepatocellular and piecemeal necrosis
   Florid clinical manifestations
3. *Liver Disease*
   Chronic hepatitis, cirrhosis or both

TABLE 5.—*Chronic Liver Disease—Synonymous Terms*

Lupoid
Subacute
Plasma Cell
Chronic Active
Chronic Liver Disease in Young Women
Autoimmune
Juvenile Cirrhosis
Chronic Aggressive
Active Chronic

one frequently sees with hepatitis) and a prolonged course characteristic of a chronic aggressive lesion. The patients tend to have higher bilirubin and lower albumin levels, and more prolonged prothrombin times. (The prothrombin time is the single best clinical prognisticator in acute viral hepatitis; prolongation six seconds beyond the control usually indicates a poor prognosis). On physical examination one finds evidence of liver decompensation, ascites, and edema or hepatic encephalopathy or both.

It is important to identify this disease as a separate entity because although it presents very much like acute viral hepatitis, the prognosis is much worse. Forty-five percent of the patients will go into complete remission, 14 percent die, 8 percent evolve with chronic active liver disease, 18 percent develop chronic active liver disease with cirrhosis, and 15 percent appear to go into remission only to appear later with cirrhosis. One can suspect the diagnosis of SHN by the severe clinical abnormalities described. However, as with all forms of chronic liver disease, the specific diagnosis can be made only histologically (features described below). Often, the severity of the hypoprothrombinemia precludes biopsy, and steroid treatment must be instituted "empirically"—until the clinical situation permits biopsy for confirmation.

I would like to turn now to the important differentiation between benign persistent hepatitis

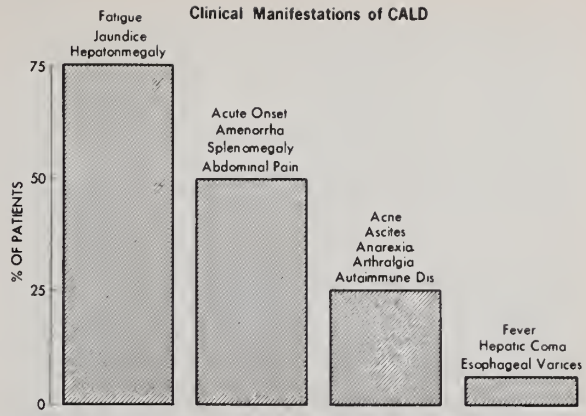


Chart 3.—Chronic active liver disease (CALD)—clinical manifestations.

and chronic active liver disease. I emphasized earlier that the patient with acute viral hepatitis should be "well" by four months. If he is not and if the results of laboratory studies remain abnormal, liver biopsy should be done. In this biopsy we are primarily interested in the differential diagnosis—BPH (not requiring treatment) and CALD (requiring steroid). Both of these entities may present as transaminasemia, thus they may be indistinguishable on the basis of laboratory data alone.

Benign Persistent Hepatitis

The features of benign persistent hepatitis are summarized in Table 3. Patients with BPH present with elevations of serum transaminase and with minor if any clinical symptoms, and the lesion is not progressive, and does not evolve into cirrhosis or portal hypertension.[6] The lesion is persistent, lasting at least six months, and may go on indefinitely. The SGOT level may wax and wane. Histologically we see portal and focal parenchymal inflammation.

Chronic Active Liver Disease

In contrast, the features of chronic active liver disease are summarized in Table 4. This lesion is aggressive and progressive, usually accompanied by a pronounced elevation of transaminase and hyperglobulinemia.[7] Significant symptoms and physical findings are often found (Chart 3) although, as mentioned previously, some cases are clinically indistinguishable from AVH or BPH and can only be identified by biopsy.

Unfortunately, considerable semantic confusion has existed in the literature. Table 5 lists some of the terms applied to this disease. It is important

to recognize that for practical purposes all of these entities are the same.

Chart 4 summarizes the biochemical and immunochemical abnormalities in CALD. Note particularly the high incidence of positive tests for smooth muscle antibody (an important marker in CALD) and the occurrence of positive lupus erythematosus (LE) cell preparations. These patients do not have systemic lupus erythematosus (the term "lupoid hepatitis" is misleading). This is a nonspecific immune response with the same significance as false positive VDRL and rheumatoid factor. Additionally, in some patients the presence of antimitochondrial antibody can be demonstrated, making the differentiation from primary biliary cirrhosis a difficult clinical problem which requires histological resolution. Only 20 percent of CALD patients are HBAg-positive—emphasizing our uncertainty as to cause in most cases. No satisfactory etiologic classification is available. Arbitrarily, we identify four groups of patients: (1) those with hepatitis B antigenemia (viral CALD); (2) those taking drugs (α-methyldopa (Aldomet®), oxyphenisatin) known to cause a histologically indistinguishable disease (toxic CALD); (3) those with associated disease of an "auto-immune" type (such as inflammatory bowel disease); and (4) those with none of the above ("idiopathic" CALD)—representing the majority of cases. From a practical standpoint, with the exception of withdrawal of the offending drug in group 3, all groups are treated alike.

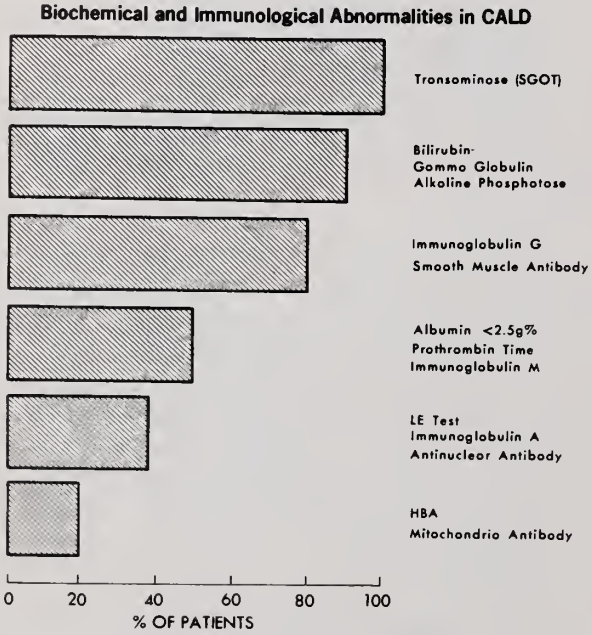


Chart 4.—Chronic active liver disease (CALD)—biochemical and immunological abnormalities.

As I have repeatedly emphasized, the presence of physical, biochemical or immunochemical stigmata may separate the transaminasemic patient with an aggressive lesion (CALD) from the one with a benign lesion (AVH or BPH). However, one cannot overemphasize the importance of the liver biopsy in differentiating these entities. Without biopsy, one cannot be certain of the diagnosis. The findings in BPH have been mentioned. Table 6 lists the spectrum of histologic abnormalities seen in CALD. Dr. Montgomery will detail these later.

TABLE 6.—*Spectrum of Morphologic Features in CALD*

	Percent of Cases
Chronic active hepatitis	22
Subacute hepatitis	
a. with bridging necrosis	27
b. with multilobular necrosis	24
Cirrhosis with active hepatitis	27
Additional findings	
a. Cholangiolitic features	8
b. "Acute viral" features	42

Fortuitous Transaminasemia

Before discussing the treatment of these entities, I would like to mention one other group of

TABLE 7.—*Primary and Secondary Treatment Programs for SHN and CALD*

	Dosage of Prednisone	
Regimen	*Alone*	*Combined with Azathioprine, 50 mg Daily*
Initial	60 mg daily for one week 40 mg daily for one week 30 mg daily for 2 weeks	30 mg daily for one week 30 mg daily for one week 15 mg daily for two weeks
Maintenance*	20 mg daily	10 mg daily
Remission	Discontinue, with gradual dosage reduction over six weeks	Discontinue, with gradual dosage reduction over six weeks
Relapse	Initial schedule	Initial schedule

*Until clinical, biochemical and histologic resolution has occurred

problem cases—those in which there is fortuitous transaminasemia. This group includes the patients who are found on routine, often preoperative, laboratory study to have an elevation of SGOT. These patients should be examined carefully for stigmata (physical and chemical) of chronicity; and if the stigmata are found, liver biopsy is indicated at that time. If the increased SGOT is the only abnormality found, the tests should be followed serially, with the patient abstaining from alcohol and hepatotoxic drugs. Persistent elevation requires liver biopsy to rule out an aggressive lesion.

Treatment

We have now identified the patients requiring treatment—those with histologically aggressive lesions (SHN and CALD). Table 7 presents the primary and secondary treatment programs. Prednisone alone is the treatment of choice; the combination program with azathioprine is reserved for patients who cannot tolerate the side effects of high-dose steroids, or those in whom there are contraindications to the required doses of steroids, such as diabetes mellitus or a history of duodenal ulcer disease.[8] The complications of liver disease are, of course, treated by standard methods. Prednisone is continued to the point of clinical, biochemical and histological remission, usually for one to two years, and then tapered. Approximately 50 percent of patients have relapse, requiring a repeat of the full course of treatment. There are some data which indicate that patients who have cirrhosis at the time of diagnosis of chronic active liver disease have the poorest prognosis for response to therapy.[9]

Treatment of these diseases has been shown to significantly reduce morbidity and early mortality.[8] It is too soon to know whether the progression to cirrhosis or the long-term mortality is affected by treatment.

In summary, I have reviewed (1) the natural history of acute viral hepatitis, (2) the warning signals for identification of the patient with chronic hepatitis, (3) the clinical, biochemical and immunochemical differentiation of the benign and aggressive forms of chronic hepatitis, (4) the treatment of the aggressive diseases.

DR. MONTGOMERY:* With that information in mind, let us now review the biopsy studies of specimens from the liver of this particular patient.

*Carolyn K. Montgomery, MD, Assistant Professor of Pathology and Radiology.

Figure 1.—Low-power photomicrograph of first liver biopsy, July, 1970; hemotoxylin and eosin stain.

Figure 2.—Reticulin stain of liver biopsy, July, 1970.

Figure 1 is a low-power photomicrograph of the first needle biopsy in July, 1970, about four months along in the course of illness. There are several very striking features. The specimen is exceedingly cellular, much more so than normal, and one sees focal aggregates of chronic inflammatory cells. There seems to be blurring of the normal architecture, and one's initial impression might well be acute viral hepatitis with lobular disarray. The broad, pale-staining, rather acellular areas are disquieting, as they raise the spector of extensive confluent or "bridging" necrosis between portal tracts and central veins. Indeed, a reticulin stain (Figure 2) shows approximation and collapse of fibers, the sequel of liver cell necrosis and dropout in those areas.

On higher magnification, one sees piecemeal necrosis (Figure 3). This process is one of inflammatory infiltration by lymphocytes and plasma cells which essentially are destroying the limiting

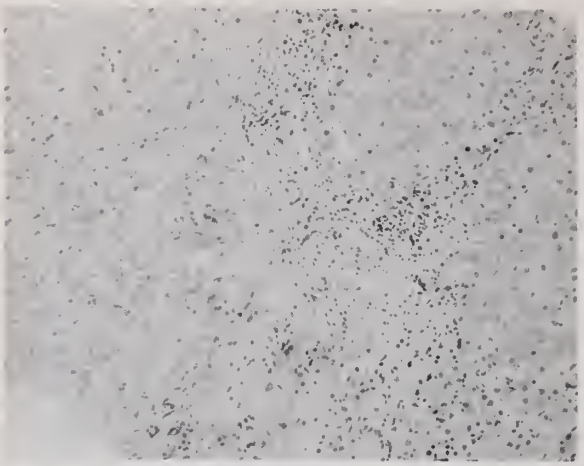


Figure 3.—Higher power photomicrograph of liver biopsy, July, 1970; hemotoxylin and eosin stain.

Figure 5.—Low-power photomicrograph of repeat liver biopsy, January, 1973.

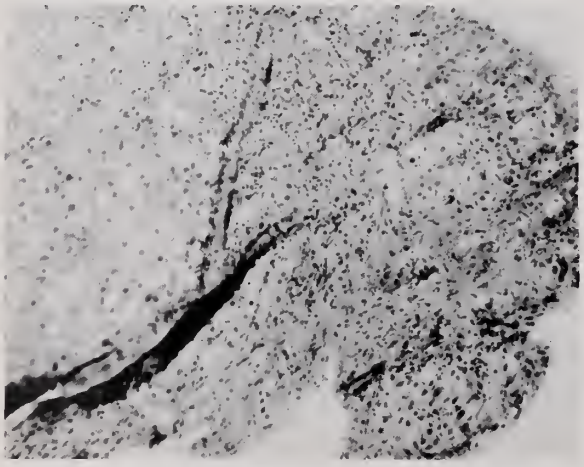


Figure 4.—Trichrome stain, higher power photomicrograph of liver biopsy, July, 1970.

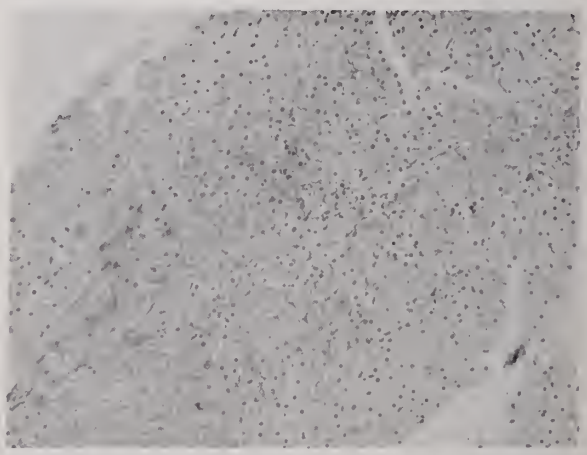


Figure 6.—High-power photomicrograph of liver biopsy, January, 1973, reticulin stain.

plate. You will notice that this obscures the normally clearcut distinction between portal area and parenchyma. There is ballooning and hydropic degeneration of liver cells with small groups seemingly split off or "dissected" from the parent lobule. Unfortunately, this process can be seen in both acute and chronic aggressive hepatitis as well as in cirrhosis. It is not an identifying feature of benign persistent hepatitis.

There are two main features which identify this case as one of chronic aggressive hepatitis. The most active degree of cellular degeneration, necrosis and inflammation is confined to the limiting plate area. If one looks deeper in the lobule, liver cells are far less involved and appear near-normal. By contrast, diffuse involvement is the rule in acute viral hepatitis. Moreover, the pale-staining areas represent more than the simple necrosis and cell dropout which would be seen in acute lesions. A trichrome stain (Figure 4) shows abundant scar, collagenous fibers "dissecting" into and distorting the hepatic lobule. This architectural distortion and active fibroplasia distinguish chronic aggressive hepatitis from acute as well as benign persistent hepatitis. In the absence of regeneration nodules, one would not think, at this stage, of cirrhosis.

We now see in Figure 5 the needle biopsy specimen from January, 1973. This is not nearly as cellular as before; the inflammation has clearly subsided and is now confined to what appear to be scattered portal tracts. Piecemeal necrosis can still be identified in some areas, and the limiting plates have a serrated, uneven appearance.

Three disturbing features point to the probability of macronodular cirrhosis: fragmentation

of the specimen, sweeping bands of delicate fibrosis about the edge of some fragments and a disorderly reticulin pattern within the parenchymal fragments (Figure 6). The diagnosis of macronodular cirrhosis may actually be missed and is notoriously difficult on needle biopsy if one chances to sample large regenerative nodules which closely mimic normal hepatic architecture. In summary, this patient has progressed from chronic active liver disease to an evolving cirrhosis.

Trade and Generic Names of Drugs

Diabinese® ..... chlorpropamide
Imuran® ..... azathioprine
Aldomet® ..... α-methyldopa

REFERENCES

1. Krugman S, Giles JP, Hammond J: Infectious hepatitis: evidence for two distinctive clinical, epidemiological and immunological types of infection. JAMA 200:365-373, May 1967

2. Shulman NR: Hepatitis-Associated antigen. Am J Med 49: 689-692, Nov 1970

3. Blumberg BS, Sutnick AI, London WT: Australia antigen as a hepatitis virus. Am J Med 48:1-8, Jan 1970

4. Nielsen JO, Dietrickson O, Ellig P, et al: Persistence of Australia antigen and development of chronic hepatitis. N Engl J Med 285:1157-1160, Nov 1971

5. Boyer IL, Klatskin G: Pattern of necrosis in acute viral hepatitis: prognostic value of bridging (subacute hepatic necrosis). N Engl J Med 283:1063-1071, Nov 1970

6. Becker MD, Schever PJ, Baptista A, et al: Prognosis of chronic persistent hepatitis. Lancet 1:53-57, Jan 1970

7. Mistilis SP, Blackburn CRB: Active chronic hepatitis. Am J Med 48:484-495, Apr 1970

8. Soloway RD, Summerskill WHJ, Baggenstoss AH, et al: Clinical, biochemical and histological remission of severe chronic active liver disease: a controlled study of treatments and early prognosis. Gastroenterology 63:820-833, Nov 1972

9. Baggenstoss AH, Soloway RD, Summerskill WH, et al: Chronic active liver disease: the range of histologic lesions, their response to treatment, and evolution. Hum Path 3:183-198, Jun 1972

Myasthenia Gravis

A paradox of myasthenia gravis is that lid retraction may be the presenting symptom. We think of ptosis as being the cardinal sign of myasthenia gravis; under certain circumstances lid retraction is the presenting sign . . . It occasionally happens that the superior rectus is involved or the muscles for upward gaze are involved more than the lids, and there's so much effort that's put into looking upward that a person gets a retraction of the lid secondarily—so it's a reasonable paradox.

—David G. Cogan, MD, *Boston*
Extracted from *Audio-Digest Ophthalmology,* Vol 11, No. 15, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Important Advances in Clinical Medicine

Epitomes of Progress—Pediatrics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Pediatrics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Pediatrics which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pediatrics of the California Medical Association and summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities
California Medical Association, 731 Market St., San Francisco, CA 94103

Advances in Genetic Counseling

THE GENERAL PUBLIC is beginning to acknowledge the value of genetic counseling. This change in attitude is itself an advance.

Recent developments in genetic technology have been dramatic, but the major advance has been the number of well-trained medical and paramedical personnel who have become genetic counselors. Physicians, Ph.Ds, nurses, and postgraduate doctors are now being specifically trained for their various roles in genetic counseling. Other highly specialized persons such as the dysmorphologist (expert in the recognition of patterns of human malformation), the biochemical geneticist and the obstetrician geneticist have increased the efficiency, capability and scope of genetic counseling services.

The feasibility and practicality of university-based "satellite" genetic clinics have been recently established by the genetic unit at the University of California, San Francisco. This advance allows university-based genetic counselors to travel to distant areas to give genetic counseling to families who would not ordinarily have access to counseling. This method of delivery assures widespread availability of genetic counseling and is potentially applicable to many areas of the United States or other countries.

Genetically related laboratory advances continue at a rapid pace. Specific identification of each chromosome is now possible through new staining techniques which leave charactertistic banding patterns. The number of metabolic disorders that can be diagnosed continues to grow as new, reliable enzyme assays are developed. Using amniocentesis, prenatal diagnosis of over 40 metabolic disorders, as well as of the numerous chromosome aberrations can be made. Myelomeningioceles can be diagnosed prenatally by finding alpha-fetoprotein levels in amniotic fluid. Fetoscopy (visualization of the fetus via a transabdominal needle put into the amniotic cavity) will allow early second trimester fetal blood sampling and identification of gross fetal deformities.

BRYAN D. HALL, MD

NOTE: Information regarding nearest genetic counseling can be obtained from The National Foundation, 800 Second Avenue, New York, New York 10017.

REFERENCES

Finley WH, Finley SC: Genetics in pediatrics. Pediatr Ann 2: 5-100, Nov 1973

Milunsky A, Littlefield JW, Kanfer JN, et al: Prenatal genetic diagnosis. N Engl J Med 283:1370-1381, Dec 17, 1970

Exchange Transfusion

THE SUCCESSFUL USE of whole blood exchange transfusion for the treatment of erythroblastosis fetalis has encouraged its use in a variety of other clinical situations. Although it is recognized that the procedure itself, in the hands of experienced personnel, is associated with a mortality of less than 1 percent, in treating newborns with hyperbilirubinemia it remains to be established that this technique is truly effective in many of the clinical situations in which it is currently used.

The indications for exchange transfusion can be broadly grouped into two major categories. They are to change the physical properties of the blood and to remove toxic substances as rapidly as possible.

Situations in which alterations in the physical properties of the blood may be beneficial to the patient and for which exchange transfusion has been employed include the treatment of the chronic painful crisis of sickle cell anemia, the management of cerebrovascular occlusions in patients with sickle cell anemia, the reduction of very high leukocyte counts in patients with leukemia to prevent cerebral vessel occlusion, and the reduction of hyperviscosity in patients with congestive heart failure—particularly those patients urgently requiring surgical operation.

Most recently it has been proposed that exchange transfusions with reasonably fresh adult blood may be of benefit to infants with a very low birth weight or with severe respiratory problems. This proposal is based on the fact that adult blood has a lower affinity for oxygen and thus might facilitate oxygen unloading in those situations in which tissue oxygenation may be suboptimal. The use of exchange transfusion in these situations must still be regarded as experimental.

The removal of toxins can also be accomplished by exchange transfusion. It has been used in treating patients with hemophilia who have developed factor VIII antibodies and newborn infants with isoimmune thrombocytopenia. However, this procedure has been of only limited benefit. Exchange transfusion is also employed in the treatment of patients with hepatic encephalopathies, including Reye's syndrome. Again, the results of such treatment are still open to question.

The removal of drugs, particularly those that are not readily dialyzable, is another indication for exchange transfusion. Such poisons include boric acid, methyl salicylate, paranitraniline, chlorinated hydrocarbons, benzene chlorate, bromate, copper sulfate, cyanide, dicumarin, ferrous sulfate, naphthalene, phenol and thiocyanates.

Exchange transfusion also is currently being used in the management of disseminated intravascular coagulation. Its potential benefits include replacement of coagulation factors, removal of products of fibrinogen degradation, and anticoagulation. Again, carefully controlled studies are necessary to validate this approach.

FRANK A. OSKI, MD

REFERENCES

Mollison PL: Blood Transfusion in Clinical Medicine, 5th Ed. Oxford, Blackwell Scientific Publications, 1972

Gross S, Melhorn DK: Exchange trusfusion with citrated whole blood for disseminated intravascular coagulation. J Pediatr 78: 415, 1971

Childhood Poisoning: Narcotic Intoxication

CHILDHOOD POISONING remains the most common pediatric emergency and the incidence is increasing each year. One of the more serious forms of childhood poisoning, and one occurring with increased frequency, is due to a group of narcotic-like drugs which include diphenoxylate (Lomotil®), propoxyphene (Darvon®) and methadone. Diphenoxylate and propoxyphene have become accessible to children through the widespread use of these agents in treating diarrhea and pain. Methadone has become available as a result of methadone maintenance programs. Such drugs are particularly dangerous because only 8 to 10 tablets of diphenoxylate or propoxyphene, and one 10 mg tablet of methadone can cause death.

It is essential for pediatricians and emergency room personnel to recognize this form of poisoning because immediate treatment is life saving. All these drugs are potent central nervous system depressants, causing severe respiratory depression and respiratory arrest indistinguishable from morphine overdose. Clinical signs include nonreactive pupils that are pinpoint in size, coma, seizures and respiratory arrest, which may result in death.

Immediate supportive care, primarily the maintenance of adequate respiratory ventilation, is critical. This should be followed by the administration of a narcotic antagonist. Naloxone (Narcan®), the drug of choice, is given intravenously at 0.01 mg per kilogram of body weight. Unlike nalorphine or levallorphan, it does not cause respiratory depression itself. It can be used even when the diagnosis is in doubt because it will not

further depress the patient whose symptoms are due to barbiturates or other depressants.

Naloxone will promptly (within 1 to 2 minutes) and dramatically reverse the respiratory depression but its antidotal action lasts only 2 to 3 hours. The depressant effects of the narcotic-like drugs last from 24 to 48 hours. Therefore it is important to monitor the patient continuously during this period and administer repeated doses of naloxone before serious respiratory depression can reoccur.

SYLVIA H. MICIK, MD

REFERENCES

Ginsburg C: Lomotil intoxication. Am J Dis Child 125:241, 1973

Aronow R, Paul SD, Woolley PV: Childhood poisoning: An unfortunate consequence of methadone availability. JAMA 219: 321-324, Jan 17, 1972

Factors Affecting Lung Maturation

THE IDIOPATHIC RESPIRATORY DISTRESS SYNDROME (IRDS) is a disease of premature infants. It accounts for approximately 25,000 deaths per year in this country. Perhaps the disease should no longer be termed "idiopathic." According to the work of such investigators as Avery, Mead, and Gluck, it appears to proceed from a deficiency of surfactant resulting either from a delay in maturation of the alveolar lining cells producing surfactant or from a defect in release of the substance from the cell.

Using the lecithin sphyngo-myelin (L/S) ratio determination or the bubble stability test on amniotic fluid, it now has become possible to routinely determine the extent of maturation of the human fetal lung. Several conditions including maternal heroin addiction, intrauterine growth retardation, and perhaps amniotic membranes ruptured longer than 16 hours probably cause an accelerated production or release of surfactant.

Liggins showed that maturation of fetal lamb lungs could be accelerated by the antepartum administration of glucocorticoids. Liggins and Howie have published evidence that betamethasone injected into women in premature labor at least 48 hours before delivery decreases the incidence of IRDS in infants born before 32 weeks' gestation. Baden and other investigators in Montreal found no decrease in the incidence of hyaline membrane disease in infants receiving corticosteroid therapy after delivery.

However, more studies are necessary before the routine use of corticosteroids in premature labor can be recommended. In extreme situations, when delivery is inevitable before 32 weeks gestation and the L/S ratio is low or the bubble stability test negative, administration of betamethasone might be considered.

WILLARD J. BLANKENSHIP, MD

REFERENCES

Liggins GC, Howie RN: A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress in premature infants. Pediatr 50:515-525, Oct 1972

Baden M, Bauer CR, Colle E, et al: A controlled trial of hydrocortisone therapy in infants with respiratory distress syndrome. Pediatr 50:526-534, Oct 1972

Hypothalamic Factors

HYPOTHALAMIC NEUROHUMORAL control of pituitary hormone secretion has been established. There are at least nine neurohumors, with three now synthesized. Adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), luteinizing hormone (LH) and follicle stimulating hormone (FSH), are responsive to hormones from target glands which inhibit further secretion by action exerted on the pituitary, the hypothalamus, or both. Hypothalamic inhibitors for growth hormone (GH), melanocytic stimulating hormone (MSH) and prolactin compensate for the absence of negative feedback products from their target organs.

Thyroid releasing hormone (TRH), a tripeptide that has been synthesized, is effective when administered either orally or parenterally. It stimulates TSH and prolactin release and is inhibited by thyroid hormones. Clinically, TRH can be used to differentiate primary hypothalamic and pituitary causes of hypothyroidism, confirm Graves' disease, measure TSH reserve and increase milk production in cows.

Luteinizing releasing factor (LRF), a decapeptide that also has been synthesized, is capable of stimulating gonadotropic secretions. A specific follicle releasing factor (FRF) has not been identified. The prepubertal hypothalamus is inhibited by low levels of circulating sex steroids. At puberty, steroid-mediated hypothalamic maturation leads to increased LRF production and increased pituitary stores of gonadotropin. LRF stimulation then leads to a heightened release of LH and FSH. Elevated sex steroids can alter pituitary responsiveness to LRF. Clinically, some patients with hypogonadotropic hypogonadism have been found to have a deficiency of LRF rather than of LH or FSH. Prolonged therapy with LRF may be helpful in treating oligospermia and azospermia. An LRF antagonist might be useful in birth control.

Somatotropin release inhibiting factor (SRIF),

a tetradecapeptide recently synthesized, inhibits release of growth hormone and may have clinical importance in the treatment of acromegaly and juvenile diabetes mellitus.

Growth hormone releasing factor (GRF) has not yet been satisfactorily isolated or synthesized.

Corticotropin releasing factor (CRF) may act in conjunction with vasopressin to control ACTH secretion.

Melanocytic hormone releasing factor (MRF) and melanocytic hormone inhibiting factor (MIF) control MSH secretion. If the results of animal experimentation can be duplicated in man, MIF may have clinical applications in parkinsonism and depression.

The secretion of prolactin appears to be under double—prolactin releasing factor (PRF) and prolactin inhibiting factor (PIF)—hypothalamic regulation. Dopamine can decrease prolactin concentration, possibly by stimulating PIF, whereas central nervous system depressants will increase serum prolactin. PIF may have value in inhibiting undesired lactation.

STEPHEN L. KAUFMAN, MD

REFERENCES

Blackwell RE, Guillemin R: Hypothalamic control of adenohypophyseal secretions. Annu Rev Physiol 35:357, 1973

Gual C, Kastin A, Schally AV: Clinical studies with hypothalamic hormones. Recent Progr Horm Res 28:173, 1972

Schally AV, Arimura A, Kastin AJ: Hypothalamic regulatory hormones. Science 179:341, 1973

Roth JC, Kelch RP, Kaplan SL, et al: FSH and LH response to luteinizing hormone-releasing factor in prepubertal and pubertal children, adult males and patients with hypogonadotropic hypogonadism. J Clin Endocrinol Metab 37:680, 1973

Side Effects of Diphenylhydantoin in Childhood

SINCE ITS INTRODUCTION in 1938, diphenylhydantoin (DPH) has been an effective anticonvulsant in the treatment of children with generalized and focal motor seizures and, to a lesser extent, psychomotor seizure disorders. Gum hypertrophy, hirsutism, ataxia and rash are among the commonly recognized side effects of DPH. Recent studies have added to the list of known potential side effects. Other investigations have emphasized the importance of its route of administration and its interaction with other medications, as well as the value of measuring DPH serum levels in achieving effective seizure control.

Reports of rickets in children receiving long-term anticonvulsant therapy have suggested that DPH, either alone or in combination with other anticonvulsants, may significantly lower levels of serum 25-hydroxycalciferol, the biologically active form of vitamin D. Therefore, it is probably advisable for children receiving DPH to be periodically screened for rickets by x-ray studies and tests of serum calcium, phosphorus, and alkaline phosphatase. If rickets is shown to exist another anticonvulsant may be cautiously substituted for DPH or small doses of vitamin D can be administered.

The administration of DPH to a pregnant woman may affect the fetus and, therefore, the infant after birth. The risk of an infant's having a significant congenital malformation at birth is two or three times greater than the average when the mother has been given DPH for seizure control during the first trimester of gestation. Serious coagulation defects in newborn children have also been attributed to use of DPH by pregnant women. Depleted clotting factors can be rapidly restored by administration of vitamin K, however.

Following head trauma, DPH and dexamethasone are frequently used simultaneously to prevent post-traumatic seizures and brain edema. However, DPH will hasten the degradation of dexamethasone, requiring the physician to use more steroid to reduce brain swelling. Also, investigators have shown that DPH is probably of little value in suppressing seizure activity in the immediate post-traumatic period. Therefore, the simultaneous administration of DPH and dexamethasone following head trauma is not advised.

The route of administration of DPH is important. The substance crystallizes in muscle depots and causes unpredictable blood levels when it is finally absorbed. Absorption from the gastrointestinal tract is preferred although DPH may be given intravenously if proper precautions are taken.

The effectiveness of DPH is dependent on its serum concentration. Less than 10 μg per ml rarely results in seizure control while levels in excess of 20 μg per ml produce ataxia and slurred speech. The widespread availability of gas-liquid chromatography at many centers has enabled physicians to obtain highly accurate determinations of serum concentrations of DPH. Such experience has shown wide variations in the dose of DPH required in relation to body weight to reach satisfactory therapeutic levels. It is advisable to titrate poorly controlled or overmedicated patients on the basis of their serum DPH levels rather than arbitrary adjustments or selection of an alternate drug. Serum monitoring has also shown that DPH administered orally once a day will satisfactorily

maintain an adequate serum level in most patients. This fact is important to the physician who deals with forgetful or busy mothers administering DPH to a small child. Serum levels are also useful in surveillance of patients who may not be taking DPH as prescribed. Maintaining a patient's serum level between 10 and 20 μg per ml will result in better seizure control while minimizing side effects.

SANFORD SCHNEIDER, MD

REFERENCES

Borgstedt A, Bryson M, Young L, et al: Long term administration of antiepileptic drugs and the development of rickets. J Pediatr 81:9-15, Jul 1972

Hahn T, Hendin B, Scarp C, et al: Effect of chronic anticonvulsant therapy on serum 25-hydroxycalciferol levels in adults. N Engl J Med 287:900-904, Nov 1972

Monson R, Rosenberg L, Hartz S, et al: Diphenylhydantoin and selected congenital malformations. N Engl J Med 289:1049-1052, Nov 1973

Rish B, Caveness W: Relation of prophylactic medication to the occurrence of early seizures following craniocerebral trauma. J Neurosurg 38:155-158, Feb 1973

Solomon G, Hilgartner M, Kutt H: Coagulation defects caused by diphenylhydantoin. Neurology 22:1165-1171, Nov 1972

Solow E, Green J: Simultaneous determination of multiple anticonvulsant drug levels by gas-liquid chromatography. Neurology 22:540-550, May 1972

Wilensky A, Lowden J: Inadequate serum levels after intramuscular administration of diphenylhydantoin. Neurology 23:318-324, Mar 1973

The Hemolytic-Uremic Syndrome

THE HEMOLYTIC-UREMIC SYNDROME has been recognized for nearly 15 years as an important cause of acute renal failure in children. The acute "microangiopathic" hemolytic anemia, thrombocytopenia (85 percent of the cases) and acute renal failure with microthrombi in small blood vessels of the kidney led to the concept that the syndrome results from intravascular coagulation. Heparin administration was therefore widely accepted as an essential part of treatment. After nearly ten years of such use, however, a clear benefit from heparin has not been documented. At Stanford, heparin is not used in the hemolytic-uremic syndrome because of the impression that the syndrome in California is more self-limited than was initially thought, and that the risks of bleeding due to heparin are therefore not justified.

A review of the natural history of the syndrome at Stanford has shown a decrease of mortality from 40 percent to 5 percent through improved medical management without heparinization. Two items of progress have been noted. (1) There is earlier recognition of renal failure where a prodrome of crampy and bloody gastroenteritis may have initially suggested primary bowel disease. By earlier recognition, over-hydration can be avoided and the frequency of severe hypertension, heart failure and hyponatremia can be decreased. By avoiding over-hydration, necessary blood transfusions can also be given more safely. (2) Proper management of acute renal failure has further decreased the frequency of avoidable complications. Where necessary, dialysis can now be carried out in many centers. Whether heparin therapy can offer any further gains beyond those resulting from generally improved medical management has yet to be shown.

BRUCE M. TUNE, MD

REFERENCES

Lieberman E: Hemolytic-uremic syndrome. J Pediatr 80:1, 1972

Lieberman E: The value of collaberation. J Pediatr 82:363, 1973

Tune BM, Leavitt TJ, Gribble TJ: The hemolytic-uremic syndrome in California: A review of 28 cases with long-term follow-up. J Pediatr 82:304, 1973

Dobrin RS, Larsen CD, Holliday MA: The critically ill child: Acute renal failure. Pediatr 48:286, 1971

The Significance of an Unusual Odor in Infants

WITH STOKKE'S RECENT REPORT, "Beta-Methylcrotonyl-CoA Carboxylase Deficiency: New Metabolic Error in Leucine Degradation," attention is again focused on the value of an unusual odor as a clue to the diagnosis of a rare inborn error of metabolism. The patient discussed in the report had all the clinical features of Werdnig-Hoffman disease, including pronounced hypotonia, diaphragmatic breathing, tongue fibrillations, muscle wasting, absence of deep tendon reflexes and diminished mental alertness. These findings were associated with an unusual odor present in the neonatal period and reminiscent of the odor of cat urine.

The metabolic defect was shown to be an absence of activity of the biotin dependent enzyme beta-methylcrotonyl-CoA carboxylase. Results of urinalysis showed large amounts of beta hydroxy isovalerylic acid and beta-methylcrotonyl glycine in the patient's urine. However, neither of these substances has an odor resembling that of cat urine. Thus, the metabolite responsible for this odor remains unidentified. A biotin response from this disorder has been reported. Therefore, treatment should consist of administering large doses of biotin or limiting the dietary intake of leucine, or both.

Other metabolic disorders that have been reported to result in an unusual odor during the neonatal period include phenylketonuria (musty or mousy odor), maple syrup urine disease (maple

syrup odor), oasthouse urine disease (yeast-like, dried celery odor), two disorders that result in an odor of sweaty feet, the fish odor syndrome (odor of decaying fish), and the odor of rancid butter syndrome.

It is readily apparent that through the sense of smell an astute physician can diagnose some unusual disorders of metabolism and institute life-saving therapy while awaiting laboratory confirmation.

JOHN MACE, MD

REFERENCES

Stokke O, Eljjarn L, Jellum E, et al: Beta-methylcrotonyl-CoA carboxylase deficiency: A new metabolic error in leucine degradation. Pediatr 49:727-735, 1972

Sidburry JB Jr, Smith EK, Arland W: An inborn error of short chained fatty acid metabolism. J Pediatr 70:8-15, 1967

Centerwall WR, Centerwall SA: Phenylketonuria (Folling's disease): The story of its discovery. J Hist Med 16:292-296, 1961

Improved Survival of Patients with Acute Lymphoblastic Leukemia Receiving Early Central Nervous System Treatment

AS THE CHEMOTHERAPY of the hematologic manifestations of acute lymphoblastic leukemia has improved and resulted in longer survival, the incidence of central nervous system (CNS) leukemia has risen. Additionally, the appearance of leukemic cells in the CNS rather than in the peripheral blood or bone marrow as the first evidence of termination of complete remission has been reported in 30 to 60 percent of children. The presence of malignant cells in the CNS sanctuary protected from antileukemic drugs may be an important source of cells which later produce CNS symptoms and hematologic exacerbations. These statistics and hypothesis have formed the rationale for intensive early treatment and prophylaxis of the CNS and offer the hope that with eradication of this malignant cell reservoir, symptom-free survival will be prolonged further with cure a possibility.

The most successful methods of CNS treatment are (1) irradiation of the entire cranio-spinal axis with 2,400 radiation absorbed doses (RADS); (2) repeated administration of intrathecal methotrexate; or (3) a combination of cranial irradiation, 2,400 RADS, with intrathecal methotrexate. A decrease to 4.4 percent from 15 percent in the incidence of the CNS as the site of the first evidence of relapse has been achieved, and these treatment programs provide excellent evidence of long-term disease-free survival in at least 50 percent of patients. All children with acute lymphoblastic leukemia should receive CNS treatment early in the course of their disease as part of their total therapeutic program.

ARTHUR R. ABLIN, MD

REFERENCES

Hustu HO, Aur RJA, Verzosa MS, et al: Prevention of central nervous system leukemia by irradiation. Cancer 32:585-597, 1973

Holland JF, Glidewell O: Chemotherapy of acute lymphocytic leukemia of childhood. Cancer 30:1480-1487, 1972

Antiviral Agents and Their Use in Pediatrics

DRUGS THAT HAVE BEEN LICENSED as antiviral agents include thiosemicarbazone, idoxuridine and amantadine. The thiosemicarbazones are synthetic compounds that interfere with the assembly of virus particles. *In vitro* they are active against pox viruses (variola and vaccinia), and *in vivo* they have been found useful in preventing smallpox and treating vaccinia gangrenosum and eczema vaccinatum. Vomiting sometimes occurs with the use of these drugs.

Idoxuridine (IDU) is a synthetic compound that interferes with deoxyribonucleic acid (DNA) synthesis. It is active *in vitro* against certain DNA-containing viruses including herpes simplex (HSV), varicella-zoster (VZ), human cytomegalovirus (CMV), vaccinia, and adenoviruses.

These compounds are useful locally in herpes simplex keratitis and vaccinia keratitis. There is anecdotal evidence that parenterally these drugs may be useful in vaccinia, certain overwhelming VZ infections in immunosuppressed patients and certain cases of generalized HSV and CMV infections of the neonate. These compounds can cause gastrointestinal distress, bone marrow depression and skin lesions. Besides the fact that drug resistance develops during therapy, the drug is incorporated into the DNA molecule and may be carcinogenic.

Amantadine is a synthetic compound that interferes with the penetration of virus into cells. It is active *in vitro* against influenza A, parainfluenza, respiratory syncytial and rubella viruses. Although amantadine rarely has been used in patients with the congenital rubella syndrome, there is no firm evidence that its use was associated with significant long-range clinical improvement or with eradication of the virus. Its clinical usefulness has been in protecting humans against influenza A virus infection when administered before infec-

tion. Central nervous system manifestations have been observed with high doses.

Several compounds, although not licensed as antiviral agents, show antiviral activity *in vitro* and have been used *in vivo* with Food and Drug Administration approval. Cytosine arabinoside (ARA-C) is a synthetic compound that interferes with DNA synthesis. It is active *in vitro* against the herpesviruses (HSV, CMV, VZ). Evidence, although not well controlled, suggests that this compound is useful in certain cases of disseminated VZ or HSV infections in patients with immunosuppressive diseases and in certain CMV infections in children with renal homotransplants or malignancy. The only controlled study, using excessive amounts of ARA-C, does not confirm the usefulness of this drug but results may be related to the high dosage used. Cases of generalized HSV infections of the neonate and cytomegalic inclusion disease of infancy have been treated with ARA-C with variable results; this drug probably subdues but does not eradicate the viral infection. Toxicity is manifested by bone marrow depression, gastrointestinal distress, bleeding diathesis, liver dysfunction, rash, phlebitis, fever and hair loss. Adenine arabinoside (ARA-A) is a synthetic compound, similar to ARA-C, but apparently has less toxicity and produces a more prolonged antiviral effect. Clinically, ARA-A has been considered useful in certain mucocutaneous diseases caused by HSV, vaccinia and VZ as well as certain congenital CMV and severe HSV infections.

A controlled, multi-institutional study is needed to determine whether treatment with IDU, ARA-C or ARA-A is clinically effective. The present lack of clinically useful antiviral drugs is largely because agents that suppress viral replication also affect the metabolic activity of the uninfected cell.

HARRY T. WRIGHT, JR., MD

REFERENCES

Bauer DJ: Antiviral chemotherapy, *In* Heath RB, Waterson AP (Eds): Modern Trends in Medical Virology, London, Butterworth & Co., 1967, pp 49-76

Rytel MW: Currently available drugs for prophylaxis and therapy of viral infections. Drug Ther:25-31, Oct 1972

ADVISORY PANEL TO THE SECTION ON PEDIATRICS

LEON P. SMITH, MD, *Chairman, Mill Valley*
Chairman, CMA Section on Pediatrics

NORD NATION, MD
CMA Section on Pediatrics
Secretary
Los Angeles

ALEXANDER HATOFF, MD
CMA Scientific Board
Piedmont

RICHARD LEONARDS, MD
CMA Scientific Board
San Francisco

EDWARD J. OTTENHEIMER, MD
CMA Scientific Board
CMA Section on Pediatrics
Assistant Secretary
San Diego

WILLIAM D. MISBACH, MD
Encino

SAUL J. ROBINSON, MD
San Francisco

EDWARD B. SHAW, MD
CMA Scientific Board
San Francisco

ROBERT R. CHINNOCK, MD
Loma Linda University

IRVING SCHULMAN, MD
Stanford University

WILLARD J. BLANKENSHIP, MD
University of California, Davis

FREDERICK A. FRYE, MD
San Diego

DONALD R. SPERLING, MD
University of California, Irvine
California College of Medicine
CMA Scientific Board

SOLOMON KAPLAN, MD
University of California, Los Angeles

SYLVIA MICIK, MD
University of California, San Diego

JOHN DOWER, MD
University of California, San Francisco

ROBERT L. SPEARS, MD
University of Southern California
Los Angeles

BIRT HARVEY, MD
Palo Alto

MERL J. CARSON, MD
Orange

ALAN SHUMACHER, MD
San Diego

EDITORIAL

Viral Infection of the Fetus

THE HOPE that a significant reduction in the numbers of children with congenital anomalies or mental retardation can be achieved by protecting mothers from various virus infections during pregnancy is rapidly fading, as is pointed out by the participants in the Specialty Conference elsewhere in this issue of THE WESTERN JOURNAL OF MEDICINE. The case against rubella is clear although even in this situation there is increasing pessimism about the efficacy of vaccine as a deterrent. Congenital cytomegalovirus (CMV) infection is responsible for congenital malformations but the frequency, the associated factors which influence the probability of damage to the infant following maternal CMV infection and the method for control of CMV infection in pregnant women have not been elucidated. Other agents such as herpes simplex, the enteroviruses, mumps, varicella or the poxviruses may be associated with congenital defects or intrauterine infections but such occurrences appear to be infrequent. Careful study in both humans and animals of how viral infection during pregnancy may affect offspring has led to discovery of the less obvious sequelae of fetal virus infection and the description of "expanded clinical syndromes." The mechanisms by which some of these changes are brought about remain to be determined. In the Specialty Conference, St. Geme reviews possible explanations for growth retardation, neurologic damage and the interesting immunologic differences between acquired and congenital infection with CMV or rubella.

Yamauchi discusses the difficult problem of prevention or control of fetal infection and emphasizes the concern that inapparent infection in an immunized woman *may* lead to fetal damage although such an event has *not* been documented. Experiences reported by several investigators[1,2] show that infection of immunized individuals can occur as indicated by local virus replication and boosts in antibody titers but viremia has not been demonstrated. I would suggest that rather than *not* use the existing rubella vaccines because of the possibility of reinfection at some later date, the vaccine be administered not only to the young female population but under proper circumstances to a larger proportion of the susceptible women of child-bearing age. Booster immunizations can be provided at whatever interval is necessary to preclude the likelihood of viremia occurring following infection with the wild virus. The other alternative is not to use the vaccine and thus permit pregnant women to take their chances with the wild virus. Attempts to develop a vaccine that will confer long-lasting protection should be continued but available preparations should *not* be discarded in the meantime.

Control of CMV infection and its effect on the fetus is far more difficult. The isolation of CMV or even serologic evidence of a rise in specific antibody during pregnancy are not valid indications for terminating pregnancy until we can define the factors other than infection during pregnancy that determine if the fetus will be damaged. Studies that Nankervis, Kumar, Cooper and I are now carrying forward are cited to illustrate this point, although the work of many other investigators could also be used.

In a study of a population of over 1,000 young pregnant women and the products of their gestation, 16 percent of whom presented during the first trimester and 50 percent during the second trimester, it was observed that 11 percent excreted CMV in their urine on one or more occasions but that only 10 percent of these mothers delivered babies with CMV infection. None of these infants had congenital anomalies and all were clinically well. Follow-up of these infants has not been sufficient to determine whether development remains normal, but study of similar groups by the same investigators suggests that approximately 10 percent of such infants may eventually show signs of mental or motor retardation or neurologic deficit of some kind. Thus in studies of young mothers of low socio-economic status, approximately 1 in 1,000 deliver an infant infected at birth with CMV who at some time *may* show evidence of nervous system or other

abnormality. Most infants with congenital CMV infection do well.

The factors which determine which baby is born with overt evidence of cytomegalic inclusion disease (CID) or which baby develops later complications cannot be defined. There is evidence that primary CMV infection during pregnancy is more hazardous to the infant than recurrent infection, and it has been suggested that the trimester of the primary maternal infection influences the probability of effect on the fetus. Fiala states ". . . the most severe form of cytomegalovirus infection of fetus [is] probably acquired during the first 20 weeks of pregnancy . . . " Evidence to support this idea is difficult to obtain. Mims,[3] for example, contrasts CMV with rubella, pointing out that malformation of eye, ear and heart are not recorded for CMV and that with the exception of small body size, the abnormalities in CID can be classed as lesions rather than malformations and suggests that the fetus with CID is infected at a later stage of development than is the case with rubella. Haymaker,[4] studying a newborn with CID and periventricular calcification, suggested that infection took place during the fifth month of gestation. Nankervis and collaborators[5] were able to follow eight women who had documented asymptomatic primary CMV infection during pregnancy; one in the first trimester, four in the second trimester and three in the third trimester. The woman with primary CMV in the first trimester had CMV-positive blood cultures during the first and second trimesters and positive urine, throat and cervical cultures throughout pregnancy but delivered a normal, non-infected infant. The three infants born to mothers who acquired infection during the third trimester and one of the four infants born to second trimester converters had congenital CMV infection but all infants were clinically normal. Obviously, studies of this kind must be continued until "affected" babies are observed, but there is the indication that primary CMV *late* in pregnancy may carry an increased risk of congenital infection.

The sporadic occurrence of most viral infections during pregnancy may make it difficult to show by the crude epidemiologic approaches generally used that there is an association between anomalies and intrauterine infection with various agents. Laboratory investigation of the pathogenesis of virus-induced congenital defects may provide clues as to how studies in man may be made more sensitive. For the present, rubella vaccine should be employed to minimize the occurrence of the one virus infection that is known to produce anomalies. Studies of CMV must be continued to determine how important this agent is as a cause of mental retardation or congenital malformation and if control measures are feasible.

ELI GOLD, MD
Department of Microbiology
University of the West Indies
Kingston, Jamaica, WI

REFERENCES

1. Wilkins J, Leedom JM, Portnoy B, et al: Reinfection with rubella virus despite live vaccine induced immunity: Trials of HPV-77 and HPV-80 live rubella virus vaccines and subsequent artificial and natural challenge studies. Am J Dis Child 118:275-294, 1969

2. Horstmann DM, Liebhaber H, LeVouvier G, et al: Rubella reinfection of vaccinated and naturally immune persons. N Engl J Med 283:771-778, 1970

3. Mims CA: Pathogenesis of viral infections of the fetus. Progr Med Virol 10:194-237, 1968

4. Haymaker W, Girdany BR, Stephens J, et al: Cerebral involvement in generalized cytomegalic disease in the newborn. J Neuropathol Exp Neurol 13:562-586, 1954

5. Nankervis GA, Kumar ML, Gold E: Primary infection with cytomegalovirus during pregnancy. Abstract submitted to Soc Ped Res 1974

National Health Insurance — Are We Really Ready for It Yet?

IT APPEARS to be generally accepted that this nation should have some form of national health insurance. The arguments in favor of it and the arguments against it are well known, and have worn thin. The issue is no longer whether or not, but rather it is *what* and *when*. It is disturbing to observe that there is little evidence of any real consensus as to the *what*. As to *when*, one hears that national health insurance will certainly be enacted this year, or not until next year, or not before the 1976 Presidential election. Given these uncertainties it seems reasonable to ask if we are really ready for it yet.

The record of federal intervention in health care over the last decade has not been very impressive in terms of what has been achieved to improve the nation's health. Massive programs have been imposed, often without any real discussion or advice from those most directly concerned. They turned out to be enormously expensive and have created more problems than they have solved. It seems reasonable to be appre-

hensive that a national health insurance program developed right now by the federal bureaucracy would be just one more bungling, inefficient, costly, frustrating program.

The reason that this is likely is simple. No one, in or out of government, yet has the knowledge or experience which is necessary to plan and conduct the kind of national health insurance program this country should have. Such a program must assure that the services rendered the costs will be reasonable and the funding adequate, and that the program as a whole will not prove so inflationary to the health care system itself, or perhaps even to the national economy, that it will defeat its own aims. The lack of this essential knowledge and experience is evident:

- There is not enough known and therefore much to be learned about just what should appropriately be covered by a national health insurance program. Crisis care, comprehensive care, preventive care and health maintenance are all widely used terms but they are poorly defined in terms of specific services. There is much that is not known about the need for specific services in these categories and their relationship to medical science, patient satisfaction, the nation's health and their cost-effectiveness.
- The methods of assuring quality and containing costs in medical and health care are still largely experimental. They are certainly not sophisticated. Until they are further developed there are no proven or truly adequate means of assessing the quality of services, efficiency of operations and cost effectiveness on a national scale.
- The Professional Standards Review Organizations (PSRO) and Health Maintenance Organizations (HMO) experiments, mandated by the federal government on a massive scale, have yet to be implemented. What effect they will have on the quality, cost and efficiency of health care is unknown. It is worth noting that standardization often tends to increase rather than reduce costs, and also that experience in the health-care field so far has shown that competition tends to increase rather than reduce either costs or efficiency. The effects on quality and costs of both these very far-reaching experiments remain to be seen.
- Friction within any kind of system increases costs by requiring more energy and reducing the efficiency of the system. Little study has yet been given to the possibility of reducing internal friction within the health-care system. Rather, the opposite is the case. Almost everything that either has been done or has been proposed to change the system increases the internal difficulty of doing business within it and in consequence increases costs. More study of the causes and costs of friction within the health-care system is needed.
- If the Medicaid experience is any indication, it would suggest that the well are not yet fully ready to pay adequately for the care of the sick. Unless and until they are, underfunding of almost any national health insurance program is almost certain, with all that this implies. At this writing there is little or no evidence that this factor has been studied very much, or that a satisfactory solution to the need for adequate funding has been built into the national health insurance equation.

For reasons such as these it is suggested that we are not really yet ready to embark upon any kind of massive national health insurance program. The knowledge and experience needed to design a truly workable, satisfactory and cost-effective program is not yet at hand. This lack cannot be overcome by Congress' adopting a politically acceptable proposal which may have been developed by some well-intentioned committee or by a brace of bureaucrats behind closed doors.

Fortunately there really appears to be no great need for hurry. The federal bureaucracy and the Congress as well should be aware that the public now seems to be reasonably satisfied with the present health-care system and with the way it is working. Recent public opinion polls place the so-called health-care crisis well down on the list of national priorities. Inflation, integrity in government, the energy crisis and a number of other concerns are considered to be far more important. The possible effect of an ill-conceived national health insurance program on inflation if costs are not to be overlooked, and the inflationary effect of Medicare and Medicaid on health care costs, if not the national economy, should not be forgotten.

We have no basic quarrel with national health insurance. It is needed and it will come. When it does it should be an efficient, effective, adequately funded and fully satisfying program. But we submit that we are not really ready for it yet. There is need to gain a great deal more knowledge and experience before starting out, and things being as they are today, there is still time to do this.

—MSMW

CASE REPORTS

Refer to: Sanfelippo ML, Benson LE, McCullough DL: Functional recovery in older patients after prolonged oliguria. West J Med 120:410-412, May 1974

Functional Recovery in Older Patients after Prolonged Oliguria

MARY LU SANFELIPPO, MD
LARRY E. BENSON, MD
DAVID L. McCULLOUGH, MD
La Jolla, California

PROLONGED OLIGURIA after the onset of acute renal failure has been associated with a poor prognosis for recovery as shown by two large series of cases by Maher[1] and by Balslöv and Jörgensen.[2] Others have implicated age and the incidence of infection as factors negatively affecting the potential for recovery.[3,5] Recent reports of recovery after prolonged oliguria, such as that of Siegler,[4] emphasize the importance of early diagnosis and aggressive dialytic treatment as the basis for increasing the possibilities for return of renal function. We here report our experience with recovery of renal function after oliguria of more than 75 days in two patients who received early and frequent hemodialysis. Renal recovery, although incomplete, was sufficient to obviate the need for continued dialysis. This experience emphasizes the importance of continued, aggressive dialysis in the face of prolonged oliguria.

Reports of Cases

CASE 1. A 60-year-old white man was transferred to University Hospital, San Diego, two days after left nephrectomy for hypernephroma. At operation, neoplastic growth was noted to extend directly into the inferior vena cava with metastatic tumor in one periaortic lymph node. Postoperatively urine output was 500 ml the first day, 250 ml the second day and negligible thereafter. On the day of transfer blood urea nitrogen (BUN) had risen to 58 mg and serum creatinine to 5.6 mg per 100 ml, hemoglobin was 14.4 grams per 100 ml and hematocrit 41 percent. By the sixth postoperative day BUN was 136 mg and serum creatinine greater than 10 mg per 100 ml. An excretory urogram showed a poorly functional right kidney 15.3 cm in length. Hemodialysis was instituted when a vascular access had been placed. Hemodialysis was required 25 times during 79 days of oliguria. At that point functional recovery was sufficient to allow discontinuation of dialysis. Nine days later the creatinine clearance was 18 ml per min. On the 138th postoperative day BUN was 55 mg and serum creatinine 5.5 mg per 100 ml. A second intravenous pyelogram at that time showed the right kidney to be 12.4 cm in length. Six months after operation, a 24-hour creatinine clearance was 27 ml per minute. The patient has returned to work.

CASE 2. A 45-year-old Mexican man was the victim of an accident on the freeway and was hypotensive on admission to the hospital emergency room on July 15, 1972. On examination he was found to have pelvic and lower extremity fractures, right hemi-facial avulsion and multiple intra-abdominal injuries. Despite blood pressure stabilization with fluid administration, urine output remained less than 15 ml per hour. Initial laboratory data included BUN 23 mg per 100 ml, serum creatinine 2.3 mg per 100 ml, serum sodium 142 mEq per liter, potassium 2.8 mEq per liter, chloride 109 mEq per liter, bicarbonate 16 mEq per liter, creatine phosphokinase 22,000 IU per liter (normal 50 to 150) and confirmed the presence of myoglobinemia. An intravenous pyelogram showed a normal urinary tract.

By the fourth hospital day, BUN was 120 mg per 100 ml, serum creatinine 10.7 mg per 100 ml and creatinine clearance 6.4 ml per minute.

From the Departments of Medicine and Surgery, University of California, San Diego, School of Medicine, La Jolla.

Submitted, revised, January 21, 1974.

Reprint requests to: M. L. Sanfelippo, MD, Department of Medicine, University of California, San Diego, School of Medicine, P.O. Box 109, La Jolla, CA 92037.

Hemodialysis three to four times per week was required to control azotemia. Management of hyperkalemia required supplementary sodium polystyrene sulfonate. The patient's course was complicated by bilateral pleural effusions secondary to chest trauma, pseudomonas pneumonia, sepsis and acute cholecystitis. An open renal biopsy, performed on the 62nd hospital day as a prognostic guide to recoverability of renal function, showed tubular epithelial cell regeneration and normal glomeruli. A total of 32 hemodialyses were required during a period of oliguria lasting 85 days. Thereafter urine volume increased. On the 92nd hospital day, creatinine clearance was 10 ml per minute. Six weeks later BUN was 25 mg per 100 ml with serum creatinine of 1.3 mg per 100 ml. A series of plastic surgical procedures were begun as an essential aspect of patient rehabilitation. Nine months from the time of injury creatinine clearance was 51 ml per minute with BUN 14 mg per 100 ml and creatinine 1.4 mg per 100 ml. The patient has returned to his activities at home.

The clinical course of these two patients with respect to duration of hemodialysis and level of creatinine clearance during the period of follow-up is represented in Chart 1. The first day of oliguria coincides in each case with that of the renal insult, although in Case No. 1 the patient had a 500 ml urinary output during the first 24 hours, less than 400 ml per 24 hours being the usually accepted definition of oliguria.[2,8]

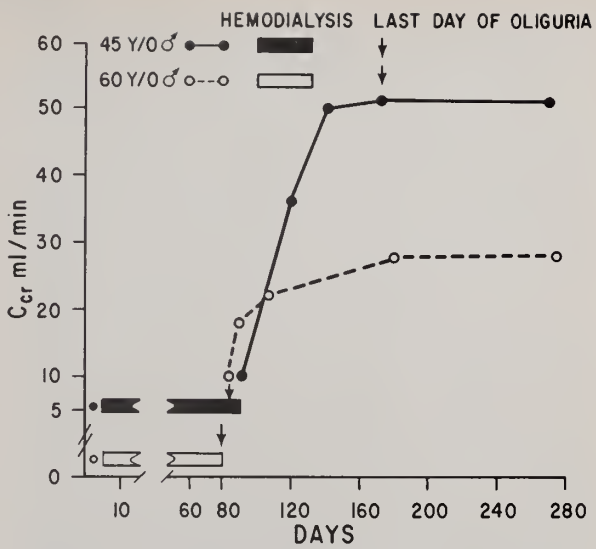


Chart 1.—Duration of hemodialysis support and recovery of creatinine clearance for the two patients is related to the number of days from initial oliguria.

Discussion

Recovery of renal function after acute renal failure usually occurs in 8 to 21 days. A case of acute renal failure with oliguria persisting for 181 days has been reported by Maher,[1] although in the same study the author emphasized that not many patients survive prolonged oliguria. Renal failure or oliguria persisting for more than three to four weeks has in some centers been an indication for renal biopsy to assess histologically the potential for recovery. In Eales's[6] report of 148 patients with acute renal failure, he stressed the diagnostic problem of distinguishing between recoverable acute tubular necrosis and bilateral massive cortical necrosis in oliguria of more than three week's duration. Renal biopsy incidence of cortical necrosis and the radiographic demonstration of renal calcification were helpful prognostic guides. Collins' group[7] used serial renal biopsies of a patient with ethylene glycol intoxication to document histologic recovery, an important element in their decision to continue dialysis.

Over the last dozen years, the increased availability of peritoneal and hemodialysis has made it possible to provide support for patients in acute renal failure through prolonged periods of oliguria. Several recent reports[4,5,8-10] have recounted cases of survival and partial or complete recovery despite prolonged oliguria. The mortality rate in such series has nevertheless remained high, especially in the older age group. Kennedy[3] pointed out that a number of factors including age, incidence of infection and occurrence of gastrointestinal hemorrhage play a role in overall prognosis, but all series substantiate the inverse correlation between duration of oliguria and survival.

Balslöv and Jörgensen[2] in 1963 published a survey of 499 patients, two-thirds of whom were more than 50 years old, the largest older age series reported to date. The mean duration of anuria was 8.8 days (with a range of 1 to 51 days) for all patients in the study, and 11.6 days for patients undergoing hemodialysis. Mean duration of anuria in surviving patients was 9.2 days. Similar figures are reported by Bluemle[5] in a series in which overall mortality rate was 50 percent. Forty-two percent of the deaths occurred during the diuretic phase. These patients had had a mean duration of oliguria of 11 days as against 8.5 days in the survival group.

Classification of patients into age groups varies somewhat among reported series. Kiley[11] showed a decreased survival in patients over 40 years old

(two deaths among 19 patients less than 35 years of age compared with 33 deaths in 49 patients over 40), as did Kennedy's[3] series of 251 cases in which a mortality of 50 percent at age 45 was nearly 10 percent greater than at age 40.

Reports of patients surviving with prolonged oliguria and partial or complete recovery of renal function are increasing. Our two patients, both in the older age category by the criteria of most groups, survived renal failure with oliguria of 79 and 85 days respectively and both received early and frequent hemodialysis as support of their renal function during the long period of oliguria. Neither patient was hypovolemic or hypotensive after the initial insult. Serum calcium levels remained within the normal range. Intravenous administration of phosphates prevented hypophosphatemia in the first patient until oral alimentation was clinically feasible. Once the urine volume began to increase, functional recovery was progressive but had stabilized in both patients at six months.

Summary

Two cases of renal failure with periods of oliguria greater than 75 days are reported. Both patients recovered sufficient renal function to terminate dialysis support and return to pre-illness activity. The potential for recovery after prolonged oliguria is emphasized.

REFERENCES

1. Maher JF: Successful intermittent hemodialysis: Longest reported maintenance of life in true oliguria (181 days). Trans Am Soc Artif Intern Organs 6:123-127, 1960

2. Balslöv JT, Jörgensen HE: A survey of 499 patients with acute anuric renal insufficiency. Am J Med 34:753-764, 1963

3. Kennedy AC, Burton JA, Luke RG: Factors affecting the prognosis in acute renal failure. Quart J Med New Series XLIIX No 165, pp 73-86, Jan 1973

4. Siegler RL, Bloomer HA: Acute renal failure with prolonged oliguria—An account of five cases. JAMA 225:133-136, Jul 9, 1973

5. Bluemle LW Jr, Webster GD Jr, Elkington JR: Acute tubular necrosis. An analysis of 100 cases with respect to mortality, complications and treatment with and without dialysis. AMA Archiv Int Med 104:18-35/180-197, Aug 1959

6. Eales L, Dowdle EB, Saunders SJ: Acute renal failure: Its course and prognosis. S Afr Med J 38:251-255, Apr 18, 1964

7. Collins JM, Hennes DM, Holzgang CR: Recovery after prolonged oliguria due to ethylene glycol intoxication. Arch Int Med 125:1059-1062, Jun 1970

8. Hall JW, Johnson WJ, Maher FT: Immediate and long-term prognosis in acute renal failure. Ann Int Med 73:515-521, Oct 1970

9. Gutman RA, Hamon CB, Striker GE: Recovery after prolonged oliguria. Arch Int Med 126:914-915, Nov 1970

10. Lewers DT, Mathew TH, Maher JF: Long-term follow-up of renal function and histology after acute tubular necrosis. Ann Int Med 73:523-529, Oct 1970

11. Kiley JE, Powers SR, Beebe RT: Acute renal failure. Eighty cases of renal tubular necrosis. N Engl J Med 262:481-486, Mar 10, 1960

12. Kumar R, Hill CM, McGeown MG: Acute renal failure in the elderly. Lancet 1:90-91, Jan 1973

Refer to: Lund HG, Cleveland RJ, Greenberg LH, et al: Tricuspid valve replacement in carcinoid heart disease. West J Med 120:412-415, May 1974

Tricuspid Valve Replacement in Carcinoid Heart Disease

HAROLD G. LUND, MD
RICHARD J. CLEVELAND, MD
LOWELL H. GREENBERG, MD
MAURICE LIPPMANN, MD
MALIN R. DOLLINGER, MD
Torrance

METASTATIC CARCINOID DISEASE frequently results in significant cardiac lesions by a somewhat obscure mechanism.[1,2] These lesions are characterized by a proliferation of dense fibrous tissue on the endocardium, predominantly involving the cardiac chambers on the right side of the heart. Both the tricuspid and the pulmonic valves may be involved, with resulting insufficiency, stenosis or both.[2-5] The relatively prolonged survival of patients with metastatic carcinoid may allow time for significant cardiac lesions to develop which not only contribute to morbidity, but may actually be the principal cause of death. This report outlines the management of a patient with metastatic carcinoid tumor, including what is believed to be the first reported case of successful replacement of the tricuspid valve in this situation.

Report of a Case

A 57-year-old man began to have recurrent abdominal cramps, diarrhea and facial flushing in March 1969. The urinary 5-hydroxy-3-indoleacetic acid (5-HIAA) level was 220 mg in 24 hours (normal <9 mg/24 hr). On exploratory laparotomy in August 1969, a carcinoid tumor was noted involving three separate areas of ileum, with diffuse involvement of the liver. The involved areas of ileum were resected and a cannula was placed into the hepatic artery. Actinomycin-D (ACT-D) and 5-fluorouracil (5-FU) were infused intermittently into the cannula until it occluded

From the Departments of Surgery (Dr. Cleveland), Anesthesiology (Dr. Lippmann), and Medicine (Drs. Greenberg and Dollinger), Harbor General Hospital, Torrance; and the Department of Medicine, Little Company of Mary Hospital, Torrance (Dr. Lund).

Submitted, revised, October 23, 1973.

Reprint requests to: H. G. Lund, MD, 4305 Torrance Boulevard, Torrance, CA 90503.

in March 1970. Pronounced improvement in symptoms and a substantial decrease in urinary 5-HIAA excretion occurred during this period. Subsequently, ACT-D was administered intravenously and phenylalanine mustard was given by mouth. In January 1971, because of gastrointestinal irritation, this program was changed to intermittent oral administration of phenylalanine mustard and prednisone. There was satisfactory control of carcinoid symptoms and stable liver function during the following 15 months.

In January 1971 pedal edema occurred and was treated with thiazide diuretics. Murmurs of pulmonic stenosis and insufficiency were first noted. During the following 12 months increasing pedal edema, exertional fatigue and dyspnea developed. In February 1972 engorged neck veins, systolic hepatic pulsation and a murmur of tricuspid insufficiency were noted. The patient was treated with digoxin, furosemide and potassium chloride. Although there was considerable improvement in the pedal edema, exertional fatigue and dyspnea remained severe (Class III—New York Heart Association).

In March 1972 the patient was admitted to hospital for cardiac catheterization. Pertinent physical findings included a blood pressure of 140/65 mm of mercury and a regular pulse of 80 beats per minute. The face and neck were slightly erythematous. The jugular veins were distended at 90 degrees, and showed positive venous pulsation throughout systole. The expiratory phase of respiration was prolonged, and there were decreased breath sounds in the left lower lobe. The heart was enlarged 2 cm to the left of the midclavicular line. There was an increase in the left parasternal impulse. A Grade II/VI systolic ejection murmur was heard best at the left sternal border in the third interspace, and radiated toward the left clavicle. A Grade I/VI soft diastolic decrescendo murmur was heard best at the left sternal border in the third left interspace. A separate Grade I/VI soft pansystolic murmur, which intensified with inspiration, was heard at the fifth right interspace parasternally. The liver was palpable 5 cm below the right subcostal margin and had a systolic pulsation. The spleen was not palpable and there were no abnormal masses. Mild pretibial pitting edema was present bilaterally. Results of a complete blood count, urinalysis and liver function tests were within normal limits. The urinary 5-HIAA level was 172 mg in 24 hours. A chest radiograph showed mild cardiomegaly with normal pulmonary vasculature and a density at the left base. This density had not changed over a four-year interval following an open lung and pleural biopsy in 1968, which showed a nonspecific fibrotic reaction. The electrocardiogram showed notching of the R wave in leads V1 and V2 and low amplitude T waves in all leads. The P waves were prominent in leads II, III, and aVF, but were considered to be normal.

Pulmonary function studies showed a vital capacity of three liters (normal 4 liters/min) and a one-second forced expiratory volume of 1.6 liters per second (normal 2.8 liters), increasing to 2.3 liters per second after bronchodilators. The residual volume was 2.2 liters and the maximum breathing capacity was 70 liters per minute (normal 102 liters/min), increasing to 95 liters per minute after bronchodilators. An intravenous infusion of 2 micrograms of epinephrine induced flushing and a simultaneous decrease in blood pressure from 120/70 to 90/60 mm of mercury. The epinephrine infusion did not precipitate tachycardia or wheezing.

At the time of cardiac catheterization, the right atrial and right ventricular pressures were the same, with obliteration of the x descent in the right atrial pressure tracing (Chart 1). The right atrial and ventricular systolic pressures were 38 mm of mercury (normal right atrial systolic pressure 4 to 6 mm, normal right ventricular systolic pressure 15 to 30 mm). The end diastolic pressure was 15 mm of mercury, with a mean pressure of 21 mm in both chambers. The pulmonary artery pressure was 35/15 mm of mercury, with a mean pressure of 20 mm. The mean pulmonary artery wedge pressure was 11 mm of mercury (normal 6 to 13 mm). The cardiac output performed by the dye dilution method was 4.1 liters per minute (normal 4 to 7 liters/min). The pulmonary vascular resistance was 176 dynes sec/cm^5 (normal 100 to 250 dynes sec/cm^5). Angiographs showed a normal right ventricular outflow tract. Left ventricular contractility and wall thickness appeared normal. The left ventricular ejection fraction was 52 percent (normal 55 percent).

In June 1972, the patient was admitted to hospital for tricuspid valve replacement. Anesthetic premedication consisted of meperidine 75 mg, diphenhydramine hydrochloride 50 mg and atropine 0.6 mg. Thiopental (225 mg) was used for induction, pancuronium bromide (10 mg) for intubation, and maintenance doses of the latter

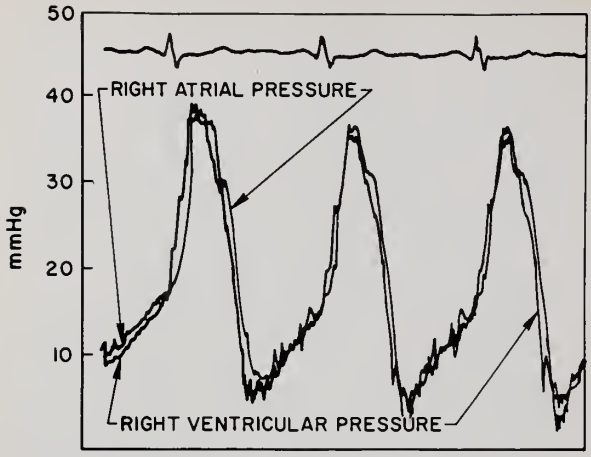


Chart 1.—Simultaneous right atrial and right ventricular pressure tracing, showing obliteration of the x descent in the right atrial pressure tracing.

given during the operation. A nitrous oxide-oxygen mixture (4 liters: 2 liters) was used for anesthesia. No hypotensive episodes occurred during the period from induction to the initiation of cardiopulmonary bypass.

Following institution of normothermic cardiopulmonary bypass and right atriotomy, the endothelial surface of the right atrium was noted to be covered by dense fibrous tissue. The endothelial surface of the right ventricle had focal involvement and the papillary muscles appeared normal. The tricuspid and pulmonary valve leaflets were thickened, deformed and retracted. The tricuspid valve was adherent to the endothelial surface of the right ventricle. The anterior and posterior leaflets of the tricuspid valve were excised and a No. 27 Bjork-Shiley mitral prosthetic valve was inserted without difficulty.

During cardiopulmonary bypass, intense erythema and swelling of the face were noted, without an elevation in venous pressure. Epsilon-aminocaproic acid (10 grams) and methylprednisolone (125 mg) were administered, resulting in a substantial but incomplete decrease in erythema and swelling within 20 minutes. Cardiopulmonary bypass was discontinued without incident.

During the first four post-operative days the patient had intermittent sinus bradycardia, alternating with a slow nodal rhythm, which was controlled with atrial pacing. He was discharged on the 21st post-operative day, doing well.

For three months following discharge his exercise tolerance improved and he was ambulatory. Anorexia and progressive weight loss then developed, as well as dyspnea. Liver function did not deteriorate and there was no evidence of congestive heart failure. He did not respond to therapy and died in October 1972, four months after tricuspid valve replacement.

At autopsy the heart weighed 340 grams. The prosthetic valve was functional and there was no overgrowth by connective tissue. The right ventricle measured up to 0.5 cm in thickness and had patchy areas of fibrosis. There were similar patchy areas of thickening of the pulmonic valve leaflets. Sections through the left ventricle showed no fibrosis or necrosis. Coronary arteries showed mild to moderate arteriosclerosis. The endocardium was thin, glistening, and grey-white. There was more than the usual degree of postoperative fibrotic reaction involving the plura.

Metastatic carcinoid was found in the liver, with multiple 0.5 to 1.0 cm tumor nodules. There was no residual carcinoid in the small bowel, nor in lymph nodes or lungs.

Discussion

Heart failure is a common cause of death in patients with carcinoid syndrome.[1,6,7] In their review of the literature, Sanders and Axtell[1] reported that the majority of patients with metastatic carcinoid disease died of congestive heart failure secondary to valvular lesions. In addition to endocardial and valvular lesions, the cardiovascular system may be compromised by the effects of various vasoactive substances present in abnormal concentrations. The specific pathological changes within the heart consist of focal or diffuse collections of fibrous tissue, free of elastic fibers, deposited on the endocardium and valve surfaces. The valves become thickened, deformed, and fixed to the underlying endocardium.[2,4,5] This process shows a predilection for the right sided cardiac valves and chambers. Left-sided cardiac lesions have been reported in association with, or in the absence of, right-sided lesions in patients with septal defects or bronchial carcinoid.[2] The fibrotic reaction and resultant deformity, however, most frequently result in tricuspid or pulmonic valvular insufficiency or both. The cause of these lesions has yet to be established, although increased blood serotonin levels have been suggested as a possibility.

Experimentally, in dogs, increased blood levels of serotonin result in pulmonary arteriolar vasoconstriction.[8] This effect seems to be of minor importance in man.[9] Other patients with metastatic carcinoid have been reported to have

normal pulmonary vascular resistance.[7,10-12] It appears unlikely, therefore, that increased pulmonary vascular resistance secondary to elevated levels of serotonin contributes significantly to right heart failure in the malignant carcinoid syndrome.

Bradykinin is a nonapeptide released from an alpha-2-globulin fraction of plasma by the action of a proteolytic enzyme, kallikrein.[13] This enzyme is found in carcinoid tumor tissue. The major pharmacologic actions of bradykinin are arteriolar vasodilation, smooth muscle stimulation, increased capillary permeability, accumulation and migration of leukocytes, and production of pain.[14] Dilation of cerebral, renal, pulmonary, and coronary vessels has been demonstrated, and may be associated with a high cardiac output. Bradykinin could thus be implicated as a contributing factor in carcinoid heart disease, since the frequent finding of a normal pulmonary artery pressure in spite of increased levels of serotonin could be due in part to the vasodilatory effect of bradykinin on the pulmonary vasculature. Elevated blood bradykinin levels have been found after epinephrine-induced flushing in patients with carcinoid syndrome,[13] and arterial kallikrein has also been seen to increase during flushing.[15]

Schwaber and Lucas[11] reported high output cardiac failure without valvular lesions, and suggested that bradykinin-induced vasodilation could be responsible. Our patient, as well as others reported, had a normal cardiac output. It is possible that different levels and proportions of vasoactive substances in various patients could be responsible for pathophysiologic variations.[16]

Regardless of the exact causes of carcinoid heart disease, well-being of the patient in the present case was greatly limited because of tricuspid valvular insufficiency. Liver function studies were stable and new metastatic lesions were not evident. Since he had a normal pulmonary vascular resistance, normal pulmonary wedge pressure, and absence of an elevated cardiac output, it was felt that the right-sided cardiac failure would be ameliorated and his system improved by tricuspid valve replacement.

Proper selection of drugs used in anesthetic management is important. Selection should be based on an understanding of the effects of these agents on the elaboration of vasoactive substances by the carcinoid tumor. Premedication with an antiserotonin drug is important. Hypotension should be especially avoided, since it may result in increased blood levels of bradykinin, secondary to epinephrine release. Certain catecholamines, particularly nor-epinephrine, epinephrine, and metaraminol, stimulate release of bradykinin and should be avoided. Angiotensin and methoxamine do not appear to stimulate bradykinin release and are the vasopressors of choice should hypotension occur. A muscle relaxant which does not result in agitation or excessive muscle fasciculation should be used, in order to prevent increased intra-abdominal pressure, with release of vasoactive substances. Pancuronium bromide is suitable for this.

The early result of the surgical procedure has emphasized that patients with valvular disease secondary to metastatic carcinoid disease may successfully undergo cardiopulmonary bypass and valve replacement without undue risk.

Summary

A 57-year-old man had metastatic carcinoid tumor with the carcinoid syndrome. Hepatic metastasis and the carcinoid syndrome were successfully controlled with chemotherapy for three years. After cardiac catheterization showed tricuspid insufficiency as the principal cardiac lesion, the patient underwent tricuspid valve replacement. Careful attention was given to the selection of anesthetic agents and drugs used in the operative and postoperative period. The cardiac symptoms improved following the surgical operation. This appears to be the first reported patient with carcinoid heart disease to have successfully undergone tricuspid valve replacement.

REFERENCES

1. Sanders RJ, Axtell HR: Carcinoids of the gastrointestinal tract. Surg Gyn & Obs 119:369-380, 1964
2. Roberts WC, Sjoerdsma A: The cardiac disease associated with the carcinoid syndrome—Carcinoid heart disease. Am J Med 36:5-34, 1964
3. Cost J, Cates JE, Pugh DW: Carcinoid heart disease. Br Heart J 21:369-380, 1959
4. Gould SE: Pathology of the Heart, 2nd Ed. Springfield, Ill. Thomas, 1960
5. MacDonald RA, Robbins SA: Pathology of the heart in the carcinoid syndrome. Arch Path 63:103-112, 1957
6. Waldenstrom J, Ljungberg E: Studies on the functional circulatory influence from metastasizing carcinoid tumors and their possible relation to enteromial production. Acta Med Scand 152: 293-309, 1955
7. Wright PW, Mulder DG: Carcinoid heart disease—Report of a case treated by open heart surgery. Am J Cardiol 12:863-868, 1963
8. Goodman LS, Gilman A (Eds): The Pharmacologic Basis of Therapeutics. New York, Macmillan, 1970
9. Grover RJ, Olson SU, Blount AS Jr: Pulmonary vascular response to serotonin in man. Clin Res 6:62, 1958
10. Gable AJ, Ray DR, Hurson R, et al: Acquired heart disease with argentaffin carcinoma. Br Heart J 18:544-552, 1956
11. Schwaber JR, Lukas DS: Hyperkinemia and cardiac failure in the carcinoid syndrome. Am J Med 32:846-853, 1962
12. Thorson A, Nordenfelt O: Development of valvular lesions in metastatic carcinoid disease. Br Heart J 21:243-248, 1959
13. Oates JA, Melmon KL, Sjoerdsma A, et al: Release of a kinin peptide in the carcinoid syndrome. Lancet 1:514-517, 1964
14. Lewis GP: Pharmacological actions of bradykinins and its role in physiologic and pathologic reactions. Ann NY Acad Sci 104:236-249, 1963
15. Melmon KL, Gillespie L Jr, Sjoerdsma A, et al: Implication of the kallikrein system in production of the carcinoid flush. J Clin Invest 43:1308, 1964
16. Dollinger MR, Gardner B: Newer aspects of the carcinoid spectrum. Surg Gyn & Obs 122:1335-1349, 1966

Refer to: Singer PA, Mestman JH, Manning PR, et al: Hypothalamic-hypothyroidism secondary to Sheehan's syndrome. West J Med 120:416-418, May 1974

Hypothalamic-Hypothyroidism Secondary to Sheehan's Syndrome

PETER A. SINGER, MD
JORGE H. MESTMAN, MD
PHIL R. MANNING, MD
JOHN T. NICOLOFF, MD
Los Angeles

THE RECENT AVAILABILITY of synthetic thyrotropin releasing hormone (TRH) for clinical testing has provided evidence that certain disorders affecting the hypothalamus or the hypothalamo-hypophyseal-portal system can lead to deficiencies in pituitary trophic hormone secretion. Indeed, some heretofore suspected primary pituitary lesions are now thought to be due to abnormalities in secretion of hypothalamic releasing factors.[1,2] Hypothalamic hypothyroidism, a condition characterized by low plasma thyroxine (T_4) and thyrotropin (TSH) concentrations, with normal TSH responsiveness to exogenous TRH administration, has been described recently in a variety of destructive lesions of the hypothalamus.[3-5] Also, patients with various congenital disorders, including nongoitrous cretinism[6] and idiopathic dwarfism[2] have been reported as having hypothalamic hypothyroidism as well.

This report describes the first known case of hypothalamic-hypothyroidism in a patient with Sheehan's syndrome, a disorder thought to be characterized primarily by hypopituitarism secondary to postpartum necrosis of the pituitary gland.

From the Departments of Medicine and Obstetrics and Gynecology, University of Southern California School of Medicine and the Los Angeles County-USC Medical Center, Los Angeles.

Supported in part by United States Public Health Service Grants AM 11727, Research Fellowship Award AM 53093, and General Clinical Research Center Grant RR-43.

Submitted, revised, September 11, 1973.

Reprint requests to: J. T. Nicoloff, MD, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles, CA 90033.

Report of a Case

A 21-year-old woman was seen at the Clinical Research Center of the Los Angeles County-USC Medical Center with an 18-month history of progressive fatigue, anorexia, a 30-pound weight loss, loss of libido, amenorrhea, and loss of axillary and pubic hair. The symptoms had begun shortly after a full-term pregnancy had had to be terminated by cesarean section because of cephalopelvic disproportion. Two units of whole blood had been transfused at that time. There was failure of lactation portpartum.

On physical examination at the time of admission to hospital in 1969 the patient was thin and appeared to be chronically ill. Pulse rate was 72 beats per minute, respiratory rate 16 per minute, blood pressure 90/60 mm of mercury, and temperature 36.8°C (98.2°F). Pertinent physical findings included dry skin, delayed deep tendon reflexes, and absence of axillary and pubic hair. The visual fields were normal employing a red test object. Laboratory tests showed a hemoglobin of 10.3 grams per 100 ml, normal results of urinalysis, serum glucose of 72 mg per 100 ml, blood urea nitrogen (BUN) 9 mg per 100 ml, and normal serum electrolytes. Elevation of pituitary trophic hormones included assessment of immunoreactive growth hormone[7] reserve following insulin induced hypoglycemia, measurement of corticotropin (ACTH) reserve by detecting the change in 24-hour excretion of urinary ketogenic steroids[8] before and following the administration of methopyrapone, measurement of urinary bioassayable gonadotropins,[9] and assessment of immunoreactive plasma TSH.[10] Deficiencies in all of the pituitary trophic hormones were observed (Table 1). Other endocrine studies included measurement of serum thyroxine[11] and free thyroxine,[12] and the results were consistent with the diagnosis of hypothyroidism. A normal thyroidal response to exogenous TSH administration in the presence of a low plasma TSH level confirmed the presence of secondary hypothyroidism. Skull x-rays were normal including the sella turcica.

Therapy with thyroxine, 0.2 mg daily, and hydrocortisone, 20 mg daily, produced a satisfactory clinical response. The patient had a single menstrual period following three months of therapy and became pregnant again. Following a full-term pregnancy, a healthy child was delivered by cesarean section and the patient subsequently, without medical advice, discontinued taking her

TABLE 1.—*Endocrine Function Tests Following Pregnancies*

	Post First Pregnancy	*Post Second Pregnancy*	*Normal Values*
Plasma Growth Hormone			
Baseline	1.8 ng/ml	2.0 ng/ml	<10.0 ng/ml
Maximum*	4.0 ng/ml	<2.0 ng/ml	<10.0 ng/ml rise above baseline
Plasma Cortisol			
Baseline	N.D.†	<1.0 μg/100 ml	5-15 μg/100 ml
Maximum*	N.D.	2.0 μg/100 ml	10.0 μg/100 ml rise above baseline
Urinary 17-Ketogenic Steroids			
Baseline	4.0 mg/24 hrs	4.3 mg/24 hrs	6-16 mg/24 hrs
After Methopyrapone‡	6.6 mg/24 hrs	6.6 mg/24 hrs	3.0 mg/24 hrs × baseline
After ACTH§	N.D.	22.3 mg/24 hrs	3.0 mg/24 hrs × baseline
Urinary Gonadotropins	6-16, 6-16 mu/24 hrs	<6, 6-16 mu/24 hrs	16-50 mu/24 hrs
Serum TSH			
Baseline	1.2 μu/ml	1.1 μu/ml	<10.1 μu/ml
After TRH	N.D.	21.3 μu/ml	6.8-31.2 μu/ml
Serum Thyroxine¶	2.1 μg/100 ml	2.0 μg/100 ml	3.0-7.0 μg/100 ml
Free Thyroxine	0.9 mμg/100 ml	0.9 mμg/100 ml	1.0-2.3 mμg/100 ml
24-Hour Thyroidal RAIU			
Baseline	8 percent	8 percent	10-34 percent
After TSH‖	28 percent	19 percent	

*Following insulin-induced hypoglycemia.
†Indicates not done.
‡Methopyrapone, 750 mg orally every 4 hours for 12 doses.
§Synthetic ACTH, 25 units in 500 ml saline given I.V. over 8-hour period for 3 consecutive days.
¶Expressed as thyroxine iodine (performed by BioScience Laboratories, Van Nuys, California).
‖10 Units bovine TSH I.M. for 3 consecutive days.

medications. Several months later she was again admitted to the Clinical Research Center for recurrent symptoms of fatigue, weight loss and lack of libido. The patient did not lactate following the second pregnancy, and there was no resumption of menstrual periods.

Repeat hormonal determinations, which now included the plasma cortisol[13] response to insulin induced hypoglycemia, and the adrenal gland response to exogenously administered ACTH, indicated that there was persistence in deficiencies of anterior pituitary hormones (Table 1). Synthetic TRH, 500 μg, was administered intravenously in a single bolus and a normal TSH response to TRH stimulation was observed (Chart 1). A normal six-hour water deprivation study indicated adequate functional status of the posterior pituitary antidiuretic hormone production.

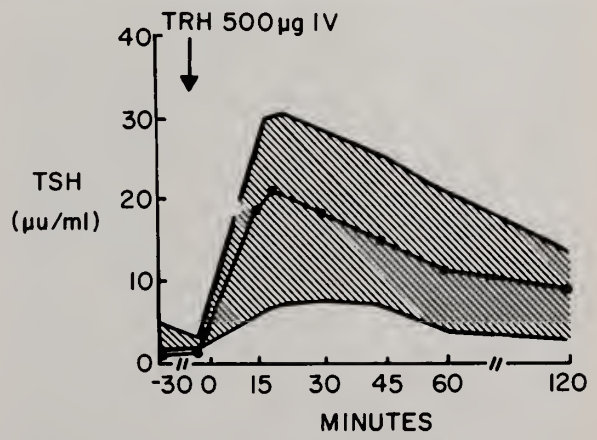


Chart 1.—TRH administration produced a normal plasma TSH response, depicted by the solid line connecting the dots. The shaded area represents the range of TSH responses to TRH observed in 23 normal subjects.

Discussion

The clinical findings and the results of the initial hormonal investigations in this patient were consistent with the diagnosis of Sheehan's syndrome with secondary hypothyroidism. However, the normal TSH response to exogenously administered TRH observed following the second pregnancy suggested a suprahypophyseal cause for the hypothyroidism. Since pituitary necrosis often characterizes the pathological findings in Sheehan's syndrome,[14] it would not be expected that the thyrotrophs would be capable of responding to exogenous TRH. However, it also has been shown that the primary lesion in this disorder may occasionally involve only the blood supply of the pituitary stalk.[15] Thus, diminished secretion of pituitary hormones could occur due to a deficiency in transport of hypophysiotrophic hormones. This type of lesion would be consistent with the observation of hypothalamic hypothyroidism in our patient. Indeed, recent evidence reported from our

laboratory suggests that a number of patients with Sheehan's syndrome may have impairment in endogenous TRH reserve or transport.[16] This does not appear to be a constant finding, however, since Fleischer and co-workers[17] have reported failure of synthetic TRH to induce a TSH rise in several patients with Sheehan's syndrome.

Another interesting feature of this patient's case was that she became pregnant following the diagnosis of Sheehan's syndrome. While pregnancy has been reported with this disease, it is uncommon and implies adequate secretion of pituitary gonadotropins.[18,19] The fact that pregnancy can occur with this disorder, however, serves to underscore the observation by Sheehan[20] that the syndrome can be atypical in its presentation and involve only several pituitary trophic hormones. Also, Sheehan[14] has provided evidence that the pituitary is occasionally capable of some repair following the original injury. It is possible, then, that in our patient either some gonadotropic function was spared following the first pregnancy, or was restored enough to allow another pregnancy to occur.

The most appealing hypothesis in this particular case, however, is that the patient's underlying lesion was suprahypophyseal, with impairment in synthesis, secretion, or transport of hypophysiotropic hormones. The most compelling evidence for this is that the patient was clinically and chemically hypothyroid, had low plasma TSH levels, and responded normally to TRH administration. It appears possible then that abnormalities in secretion or transport of the other hypothalamic releasing hormones may have been the cause of this patient's hypopituitarism. The recent availability of synthetic luteinizing releasing hormone (LRH) may offer an opportunity to further characterize the lesion leading to hypopituitarism in certain patients with Sheehan's syndrome.

Summary

A diagnosis of hypopituitarism was established in a 21-year-old woman 18 months after a full-term pregnancy which was complicated by postpartum hemorrhage. Shortly after hormonal replacement therapy was begun, the patient had a single menstrual period and became pregnant again. Following an uncomplicated pregnancy and delivery of a healthy child, she discontinued her medications, and signs of hypopituitarism again developed. Hormonal testing confirmed the presence of panhypopituitarism with hypothyroidism, yet administration of 500 μg of synthetic thyrotropin releasing hormone (TRH) produced a normal plasma thyrotropin (TSH) response. These data were consistent with the diagnosis of hypothalamic hypothyroidism, and suggested a suprahypophyseal cause for the panhypopituitarism in this patient, who may have had an atypical form of Sheehan's syndrome.

ACKNOWLEDGMENT: Abbott Laboratories provided the generous supply of synthetic TRH gratis.

REFERENCES

1. Martin LG, Martul P, Connor TB, et al: Hypothalamic origin of idiopathic hypopituitarism. Metabolism 21:143-149, 1972

2. Costom BH, Grumbach MM, Kaplan SL: Effect of thyrotropin-releasing factor on serum thyroid-stimulating hormone—An approach to distinguishing hypothalamic from pituitary forms of idiopathic hypopituitary dwarfism. J Clin Invest 50:2219-2225, 1971

3. Gailani SD, Roque AL, Band P, et al: Hypopituitarism due to localized hypothalamic lesions. Arch Intern Med 126:284-286, 1970

4. Pittman JA, Grumbach SL, Kaplan JG, et al: Hypothalamic hypothyroidism (abstract). Presented at the 47th Meeting of the American Thyroid Association, Inc., Birmingham, Alabama, Oct 12-15, 1971

5. Pittman JA Jr, Haigler ED Jr, Hershman JM, et al: Hypothalamic hypothyroidism. N Engl J Med 285:844-845, 1971

6. Miyai K, Azukzawa M, Kumahara Y: Familial isolated thyrotropin deficiency with cretinism. N Engl J Med 285:1043-1048, 1971

7. Greenwood FC, Hunter WM, Glover JS: The preparation of ^{131}I-labelled human growth hormone of high specific radioactivity. Biochem J 89:114-123, 1963

8. Rutherford ER, Nelson DH: Determination of urinary 17-ketogenic steroids by means of sodium metaperiodate oxidation. J Clin Endocrinol Metab 23:533-538, 1963

9. Klinefelter HFF, Albright F, Griswold GC: Experience with a quantitative test for normal or decreased amounts of follicle stimulating hormone in the urine in endocrinological diagnosis. J Clin Endocrinol Metab 3:529-544, 1943

10. Odell WD, Wilber JF, Utiger RD: Studies of thyrotropin physiology by means of radioimmunoassay, *In* Pincus G (Ed): Recent Progress in Hormone Research. New York, Academic Press, 1967

11. Murphy BEP, Pattee CJ: Determination of thyroxine utilizing the property of protein-binding. J Clin Endocrinol Metab 24: 187-196, 1964

12. Sterling K, Brenner MA: Free thyroxine in human serum: simplified measurement with the aid of magnesium precipitation. J Clin Invest 45:155-163, 1966

13. Nugent CA, Mayes DM: Plasma corticosteroids determined by use of corticosteroid-binding globulin and dextran-coated charcoal. J Clin Endocrinal Metab 26:1116-1122, 1966

14. Sheehan HL: The repair of post-partum necrosis by the anterior lobe of the pituitary gland. Acta Endocrinol 48:40-60, 1965

15. Sheehan HL, Stanfield JP: The pathogenesis of postpartum necrosis of the anterior lobe of the pituitary gland. Acta Endocrinol 37:479-510, 1961

16. Singer PA, Nicoloff JT: Assessment of thyrotropin releasing hormone and thyrotropin-reserve in man. J Clin Invest 52: 1099-1107, 1973

17. Fleischer N, Lorente M, Kirkland J, et al: Synthetic thyrotropin releasing factor as a test of pituitary thyrotropin reserve. J Clin Endocrinol Metab 34:617-624, 1972

18. Jackson IMD, Whyte WG, Garrey MM: Pituitary function following uncomplicated pregnancy in Sheehan's syndrome. J Clin Endocrinol Metab 29:315-318, 1969

19. Martin JE, MacDonald PC, Kaplan NM: Successful pregnancy in a patient with Sheehan's syndrome. N Engl J Med 282: 425-427, 1970

20. Sheehan HL: Atypical hypopituitarism. Proc Royal Society Medicine 54:43-48, 1961

LETTERS *to the Editor*

Of Maturity in Medical Practice

To the Editor: It was cheering to read your "Carrots and Sticks" editorial (Are Carrots and Sticks for Donkeys or Doctors? West J Med 120: 237-238, Mar 1974) not only because of the full title but also because it is proper and timely, and I would hope instructive to the younger generation of physicians. However, despite its cogency, in the current worship of change and of the newest and latest both in politics and medicine itself, I have a lingering doubt of its acceptance. It appears that the rapid scientific strides in medicine of the last two to three decades spawned this assumption of the superiority of the new and devaluation of the old—the tried and proven.

I find it amusing to see occasionally in the medical literature frank reappraisals of prevalent ideas and concepts, held up as almost infallible for a period of time, and their dismissal. The old rule —proof of time and experience—still applies. That is why I put only a little stock in "continuing education" which is basically an emphasis on the newest and latest. (This is not to imply that the progress in such subjects as immunology, genetics and virology—just to mention only three new disciplines—is to be deprecated or minimized!)

There are, of course, fashions or patterns of medical outlook—fashions, like those in other aspects of living, which are popular for a time. It is difficult (and often unacceptable) for the younger physician to believe that the newest theories and postulates can be wrong. It would appear appropriate, however, not to hide this old rule from the young; it should be re-emphasized. There is often no urgent need for a headlong rush to try out the newest. It is a sign of maturity to wait a while (not a sign of ignorance!) until a true crystallization of factual knowledge is at hand. This, with particular reference not only to medicine, but also—to return to the purpose of your editorial—to politics.

Edward Palmer, MD
Lake Oswego, Oregon

Thermography in Venous Thrombosis

To the Editor: The recent specialty conference[1] and subsequent editorial[2] in the March 1974 issue of The Western Journal of Medicine aptly refers to the problem of recurrent venous thrombosis and pulmonary embolism as one of the most difficult clinical problems.

There was a fine review of currently available diagnostic methods. The editorial specifically referred to newer diagnostic and therapeutic approaches. We would like to call attention to one very promising diagnostic modality, namely, the use of thermography.

Cooke's article[3] emphasizes that one of the most constant clinical signs in deep venous thrombosis, present when other signs were either absent or equivocal, was an increase in the heat of the limb and delayed cooling on exposure. Consideration of the chemical activity in the limb accompanying and consequent on a thrombotic episode did suggest the possibility that increased heat could be present but subclinical from an early stage. Thus, a means of measuring this increased heat would possibly present a method by which deep venous thrombosis could be detected early in its development. Thermography offers such a technique. It has also the advantage of being truly non-invasive. Thermography shows the temperature difference on an object in the form of a thermal picture (grey-tone thermogram) using the natural infra-red radiation which varies with the surface temperature of the object. In our study we used the AGA thermovision system 680, which operates in a similar fashion to a closed circuit television in which a camera is coupled to a display unit. The camera unit consists of a single indium antimonide detector cooled with liquid nitrogen to attain a high sensitivity in the spectral band of 2 to 5.6 microns. Encouraged by Cooke's report, we have applied the study to 17 patients with suspected pulmonary embolus. In 15 such patients, all of whom had abnormal perfusion scans and clinical course entirely compatible with the diagnosis of pulmonary embolism,

thermography demonstrated unilateral heating of one thigh or leg. Two patients clinically suspected of having pulmonary embolism had normal lung scans and the clinical follow-up suggested that they had a different explanation for the onset of chest pain. In both patients thermography of the legs was normal. In one of these two patients there was clinical suspicion of deep vein thrombosis and a phlebogram was obtained. This demonstrated varices but no thrombosis.

Five of the 15 patients who had positive thermography and abnormal lung scans had also x-ray contrast venography which did demonstrate unilateral thrombosis in the leg or thigh veins. The thermographic examination is conducted in a room with temperature maintained around 76° and where all sources of draft are excluded, such as open windows and doors. The patient is exposed to the pubis, remains so for 10 minutes before thermographic examination, the legs at the ankles placed 4-6 inches apart and externally rotated. This procedure allows the legs to obtain thermal equilibrium with the surrounding atmosphere. The ankles are elevated slightly so that the calves are not compressed by touching the mattress, allowing an unobstructed venous return. Time taken to examine one patient is about 10 minutes for cooling and about 5 minutes to expose the different pictures.

A personal communication from Dr. Cooke[4] states that he has recently studied 100 postoperative and general medical cases with correlations between thermography and phlebography. There were only 3 discrepancies in the sense there were two false negatives by thermography and one apparent false positive.

In our limited experience, this modality represents a major advance in the diagnosis of patients with venous thrombosis and pulmonary embolism.

Jorge A. Franco, MD
Bernadine Kovaleski
Klitia Vanags
Monika Schrier
Nuclear Medicine
O'Connor Hospital Medical Center
San Jose, California

REFERENCES

1. Silvergleid AJ: Thromboembolism—Diagnosis and treatment—Stanford University School of Medicine (Specialty Conferences). West J Med 120:219-225, Mar 1974
2. Rapaport SI: Venous thrombosis—Newer diagnostic and therapeutic approaches (Editorial). West J Med 120:239-240, Mar 1974
3. Cooke ED, Pilcher MF: Thermography in diagnosis of venous thrombosis. Br Med J 2:523-526, Jun 1973
4. Cooke ED: Personal communication

Trauma Rounds

Chief Discussant
MICHAEL CHAPMAN, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is the third of a series of Conferences on Trauma at San Francisco General Hospital.

Refer to: Chapman M: Management of pelvic fractures (Trauma Rounds). West J Med 120:421-424, May 1974

Management of Pelvic Fractures

DR. JAMES TATE:* The case for today is that of a 45-year-old man who was injured when his motorcycle was struck by an automobile. On admission to hospital, his primary complaint was severe pain in the hip and pelvic area. There was no loss of consciousness at the scene of the accident and he was alert and oriented on arrival. The history was essentially noncontributory. On physical examination the patient was pale and diaphoretic. The blood pressure was 150/80 mm of mercury and pulse rate 80. Extremities were cool. No injuries were shown on examination of the head and neck area and the chest was clear to auscultation. Abdominal tenderness was noted, particularly in the suprapubic and pelvic area, and there were hypoactive bowel sounds. On rectal examination the prostate was noted to be free floating. The rectum was disrupted and there was blood on the examining finger. Blood was emerging from the urethra, and on insertion of a Foley catheter gross blood returned. There was full range of motion in all four extremities.

Intravenous pyelograms showed disruption of the bladder and total disruption of the urethra. Pelvic films showed fracture of the left acetabulum, disruption of the sacroiliac joint, separation of the symphysis pubis with craniad displacement of the left hemi-pelvis. On exploratory laparotomy a large pelvic hematoma was observed but there were no other intraperitoneal lesions. A totally diverting descending colostomy and closure of the bladder injury were carried out. Suprapubic cystostomy was done and suprapubic drains and a pack were placed in the retrorectal area to control persistent diffuse hemorrhage. Following laparotomy, bleeding continued around the rectal packs and from the rectum.

Selective arteriograms of the pelvic vessels showed that the left internal pudendal artery was a major source of the hemorrhage. Autologous clot was injected down the angiographic catheter into the left pudendal artery and this controlled the bleeding. Additional treatment consisted of placing the patient in a pelvic sling.

The following day he was returned to the operating room and the rectal packs were removed. In the intensive care unit his cardiovascular status deteriorated, as manifested by a rising pulmonary artery wedge pressure, an increase in central venous pressure and a fall in urinary output. Because of this, cardiac glycocides were administered and the vital signs improved. The following day active bleeding again developed through the suprapubic drains. On repeat exploratory laparotomy the left hypogastric artery was ligated after autologous muscle had been injected into this vessel. There was no further bleeding from this area. Following this, cardiovascular instability

*Trauma Service Intern.

Reprint requests to D. D. Trunkey, MD, University of California Service, San Francisco General Hospital, San Francisco, CA 94110.

Supported in part by NIH Grant GM 18470, and Northern California Trauma Committee, American College of Surgeons.

and rising creatine and blood urea nitrogen were noted. This necessitated placement of a Scribner shunt and the use of hemodialysis. The clinical course then gradually improved, respiratory difficulties were minimal and good renal function returned by the end of the second week after trauma. At present, four weeks after injury, the patient's general condition is excellent. Bed rest is required for the unstable fractures, and the colostomy can be closed after the wounds are completely healed.

DR. THOMAS GADACZ:* The immediate problem in this patient was control of the pelvic hemorrhage. At the time of the initial laparotomy the diffuse nature of the hemorrhage led us to attempt to control it with packs. When it persisted we used arteriograms to locate the bleeding points. The arteriograms showed persistent arterial bleeding in the left pelvic area. The vessel was identified as the internal pudendal artery. Autologous clot injected through the arteriogram catheter controlled this hemorrhage at first. However, it apparently disintegrated and the patient was returned to the operating room where autologous muscle was used to form an embolus in the left hypogastric artery. This controlled the pelvic hemorrhage.

DR. ROBERT C. LIM, JR.:† *I have the impression listening to this history that the patient was in compensated shock when he was admitted to the emergency room. Is that correct, Dr. Gadacz?*

DR. GADACZ: Yes. During laparotomy we found approximately a six-unit retroperitoneal hematoma in addition to the external blood loss through the rectum.

DR. DONALD TRUNKEY:‡ I think that this illustrates one of the main problems in management of the pelvic fracture. The pelvic fracture can be a source of considerable loss of blood into the retroperitoneum, thighs and buttocks with no overt manifestation on physical examination. In addition, there may be intraperitoneal bleeding from the pelvic vessels or from associated injury of intra-abdominal organs. For this reason, exploratory laparotomy is usually necessary in extensive injuries of this type to make sure that all overt bleeding is controlled. Disruption of the rectum and the bladder in this patient were additional indications for laparotomy.

Specific comments about this patient's injuries include the following: The retroperitoneal space is relatively avascular and fecal contamination here may cause local infection and ultimately may cause fatal sepsis. The management should consist of a completely diverting colostomy, wide drainage of the retrorectal space and irrigation of the distal rectal segment to remove all fecal contents. There is also clear indication for treating the patient with antibiotics in this situation. These are not prophylactic antibiotics, since the space is already contaminated—almost certainly infected. I favor the use of limited spectrum antibiotics as opposed to broad spectrum antibiotics which may select out resistant organisms which then can cause complicated lethal infections. High doses of penicillin are my treatment of choice and I would give 30 million units of aqueous penicillin daily.

To treat the patient's bladder injury, a two or three layer closure of the injury itself is indicated. In addition, decompression of the bladder with a suprapubic cystostomy is mandatory. Again, drains must be placed around the suprapubic area. Insertion of a Foley catheter in the urethra is essential to provide further drainage and maintain continuity of the lower genitourinary tract while healing occurs.

There has been considerable controversy as to how best to handle pelvic bleeding, which can be quite massive. Some investigators have advocated exploring all pelvic hematomas. However, most pelvic hemorrhages are venous in origin and are difficult or impossible to control, particularly since most of the vessels retract into bony structures. In addition venous bleeding can usually be easily tamponaded, especially if it is contained by the intact peritoneum. The policy that has been adopted at this hospital, therefore, is not to explore pelvic hematomas unless they are expanding or pulsatile. If hemorrhage persists, the following program should be carried out: A panel of coagulation tests should be obtained, including prothrombin time, partial thromboplastin time and a study of the platelets both on a quantitative and qualitative basis. If medical bleeding is the problem, then appropriate therapy should be given such as platelet packs, fresh frozen plasma or fresh warm whole blood.

If bleeding is not of a nature controllable by medical means, then selective angiography is called

*Chief Resident, Trauma Service.
†Coordinator in Charge, Mission Emergency Hospital.
‡Chief of Surgery, Mission Emergency Hospital.

for. This will show the site of arterial bleeding in the minority of patients in which this is the source of hemorrhage. In such a case, two choices are open. Autologous clot injected through the catheter may be used to form an embolus. Or, if the bleeding vessel is too large for this to be practical, direct exploration and ligation or repair of the vessel is warranted.

Using these criteria for exploration of the pelvic hematoma, we have had only two patients in a series of over 200 cases of pelvic fractures in the last three years who bled to death from a pelvic injury. It should be pointed out that we have not found hypogastric artery ligation in itself effective in managing pelvic bleeding because of the extensive collaterals that pelvic vessels have. It may be beneficial, however, when autologous muscle is used to form an embolus in the vessel.

Dr. Chapman, you have had considerable experience with management of pelvic fractures. What are your comments regarding this particular patient?

DR. MICHAEL CHAPMAN:* It is interesting that the cause of injury in this patient was similar to that of four other patients we have seen at this hospital recently. All four of these patients also were motorcycle riders who were involved in accidents. What appears to happen is that as the motorcycle strikes an object, the handlebar pins the leg at the groin and the victim's forward motion continues. The handlebar may actually impale the patient in the anterior perineum. With the leg trapped and the patient continuing forward, the pubic symphysis separates, producing an open-book fracture of the pelvis with disruption of the sacro-iliac joint. This patient had an acetabular fracture in addition so that the leg was almost wrenched off. Two of the other patients had a traumatic hemipelvectomy with skin and some muscle still attached.

We have recently reviewed pelvic fractures at this hospital and have devised a classification for these injuries. Its object is to enable us to examine a fracture and make some decision about prognosis, ultimate blood loss and possible injuries to associated organs as well as determining whether the fracture is stable or unstable. Unstable fractures usually require some immobilization which may interfere with pulmonary management.

*Assistant Chief of Orthopedics and Assistant Professor of Orthopedic Surgery, University of California, San Francisco, School of Medicine.

TABLE 1.—*Classification of Pelvic Fractures*

I. Comminuted (Crush) Injuries
- Three or more major components involved (rami, ilium, acetabulum, sacrum)
- Often unstable
- Usually are combinations of II—A, B, C, D

II Unstable (Require immobilization or traction to reduce hemorrhage or maintain position of weight bearing portions of pelvis.)
- A. Diametric fractures with cranial displacement of hemipelvis (Froman and Stein, 1967; Malgaigne, 1847)
- B. Diametric fractures, undisplaced
- C. Open-book (sprung) pelvis
- D. Acetabular fractures

III. Stable (Immobilization usually unnecessary except for symptomatic relief.)
- A. Isolated fractures
- B. Fractures of the pubic rami

TABLE 2.—*Relation of Type of Pelvic Fracture to Mortality and Morbidity*

	No.	*Mortality*	*Morbidity*	*Respiratory Distress Syndrome*
Type I ...	23	5(21.7%)	16(69.5%)	8(34.7%)
Type II ...	61	7(11.4%)	28(45.9%)	13(19.4%)
Type III ...	89	4 (4.5)%	27(30.3%)	7 (7.8%)

Therefore we have proposed three major types of fractures (Table 1). First is the *type I* or crush injury. This is a fracture that involves three or more of the major components of the pelvis: the pubic rami, the ilium, the acetabulum, and the sacrum and sacro-iliac joints. These fractures are usually unstable and are combinations of the various type II injuries. *Type II* fractures are unstable and have four subgroups. Type II A and B are the displaced and undisplaced Malgaigne fracture. This kind of fracture is usually due to falls. The pelvis on one side is driven cephalad, resulting in a vertical fracture through the anterior and posterior elements of one side of the pelvis. Type II C is the open-book fracture. Type II D is any fracture involving the acetabulum. *Type III* fractures are stable and usually are of little concern in the patient with multiple injuries. They are isolated fractures of the pubic rami, iliac crest or acetabulum. Our patient had a class II C pelvic fracture with tremendous associated soft tissue injury. With the acetabular fracture it could be considered a type I.

Types I and II have the greatest associated incidence of pulmonary complications and blood loss (Table 2). Mortality in this hospital and in most series is 22 percent for type I, 11 percent

for type II and 4.5 percent for type III injuries. Much of the mortality relates to the magnitude of the soft tissue injuries and to the severe associated injuries.

The stable fractures do not require any specific treatment. As soon as the acute pain and discomfort have subsided, ambulation can be begun. Type I and types II A, B and C are best treated with a pelvic sling and type II D may require skeletal traction on the femur in addition. All have a good prognosis for healing. After four weeks, stability is generally satisfactory enough that pelvic traction can be discontinued and ambulation begun a week or two afterward.

Dr. Trunkey: In summary, the principles which we wish to emphasize in this case are as follows. Pelvic fractures can be classified into three types. The stable or type III fracture involving one element of the pelvic ring has a good prognosis. The unstable type I and II injuries are fractures caused by great violence. Soft tissue injury is extensive and severe associated injuries are frequent in the type I and II injuries, with associated bleeding often a problem. Laparotomy usually is indicated to control the intraperitoneal hemorrhage or treat associated organ injury. Hematomas that are not pulsatile or expanding usually are venous in origin and are best treated by leaving the peritoneum intact so that tamponade will stanch bleeding. If there is evidence of continuing hemorrhage following initial treatment, then medical causes of continued hemorrhage should be ruled out or treated. At this point, arteriography can be of great help in determining the site of major bleeding points. Definitive ligation of the specific vessel, if large, or catheter embolism, if small, should control the hemorrhage. If bleeding is diffuse and uncontrollable by any other means, judicious placement of packs may be necessary. These should be removed after 24 hours if possible to avoid septic complications.

Refer to: Ward PD: The curious odyssey of Regional Medical Programs (Government and Medicine). West J Med 120:425-429, May 1974

The Curious Odyssey of Regional Medical Programs

PAUL D. WARD, *Oakland*

DURING ITS EIGHT YEARS of existence, Regional Medical Programs (RMP) has developed a history marked by many changes of fortune. No social program enacted after World War II has experienced the ups and downs, the changes in direction, or the praise and vilification that have befallen RMP. Some programs like Model Cities and the Office of Economic Opportunity (OEO) have peaked and then fallen from grace, but none have had the spectacular roller-coaster ride of RMP. Those involved in the program believe RMP has proven its worth and provided many improvements in the health care system, but it has also served to test the stamina of those directly involved in the program, for it has been like riding the roller-coaster through a wind tunnel with the wind direction changing every few minutes.

The changes of fortune have resulted mostly from an unusual number of changes in philosophy at the top level of the Department of Health, Education and Welfare, the multitude of quarrels HEW has had with Congress, and the intrusion of the Office of Management and Budget into program decisions (which OMB is ill-equipped to enter, especially in the health care field where its expertise barely equals zero). Finally, the courts have entered the scene, with a ruling that the program should be returned to the course charted by Congress and that the funds appropriated by Congress should be made available for the purposes of the program. If we could end the story on that note, it would be like the classical novel plot: the beginning, the problems faced in the middle, and the happy ending. But in real life, there is probably more trauma to come.

In the beginning, the intent of the legislation was to create a partnership consisting of major segments of health providers, educators, public and voluntary health agencies and other health resources. While these new "cooperative arrangements" were to be carried out with an emphasis on heart disease, cancer, stroke and related diseases, there was an implicit, though unstated, acknowledgement that the potentially confining restraints of a purely categorical approach to good health care left room for other experimental activities. In any case, the overall objective was to make high quality medical care more uniformly available to every American. For more than three years this view of Regional Medical Programs held sway: Partnerships were developing among medical centers, the health professions and facilities designed to provide a single quality of medical care largely of a categorically-linked nature through voluntary cooperative arrangements; and, without interfering with established patterns of medical practice, to disseminate new knowledge to doctors, nurses and other health professionals through programs of continuing education.

In the spring of 1970 there were stirrings in the high-reaches of the Department of Health, Education and Welfare. The department issued a set of recommended national priorities for health. Emphasis was placed on the quantity side of med-

The author is Executive Director of the California Regional Medical Program.

Submitted February 22, 1974.

Reprint requests to: P. D. Ward, Executive Director, California Regional Medical Program, 7700 Edgewater Drive, Oakland, CA 94621.

ical care, with quality relegated to a secondary role. Special effort was to be made to serve the needs of the poor, including particularly the American Indians, urban and rural poor, migrant farm families, children under five and women of child-bearing age who might not otherwise be able to receive appropriate contraceptive counseling. "Primary care" was described by national leaders in favorable terms, and was to be developed for those Americans who, for a variety of reasons, were not able to seek or find necessary medical care in their own communities.

Regional Medical Programs had been enacted as Title IX of the Public Health Service Act. With the exception of Medicare, Medicaid and Maternal and Child Health, most federal health programs are a part of the Public Health Service Act and are subject to extension by Congress at least every three years. When the Administration introduced its bill in 1969 to extend Regional Medical Programs, the emphasis on categorical programs was gone. Primary care and creation of new kinds of health care services were in the ascendancy, and the proscription against interfering with traditional patient care patterns had been deleted. Congress modified the Administration's desires, keeping the categorically-related activities, adding kidney disease, and retaining the restriction against interfering with established medical care practice patterns. Notwithstanding this sentiment, Administration spokesmen continued to speak favorably of RMP's as the proper vehicle for promoting new patterns of medical care and new forms of health manpower.

About this time, however, the practice of "forced carryover" of funds began. "Forced carryover" is federalese meaning that OMB or the fiscal people in the department embargo a part of the money Congress has appropriated for a program and carry it over to the following year, usually for the purpose of reducing the next year's appropriation. It is a means of whipping a program into line—of warning it to revamp its behavior and purposes, or perish. This revamping always proves difficult for some if it violates the intent of the law, and disturbing to others as they see their commitments to local people who are cooperating voluntarily with the program upset by the change in purpose. Also, it is a sure way to throw consternation, confusion, distrust and depression into the working ranks of a program. There is no surer way to reduce the productivity and momentum of any program, if that is the intent.

The Administration took the next step shortly thereafter by introducing its proposed budget for fiscal 1972, in which the language called for a "stronger discriminatory policy which will be applied in awarding grants to individual regional medical programs." "As a result," the budget language continued, "a sharp retrenchment in grant awards will be made for those regional medical programs which have been the least productive in order to support selected increases for those regional medical programs which have shown the greatest innovative potential for moving the local health care system toward improved accessibility and quality of care.

"The major shift in emphasis by the regional medical programs will be directed toward improved and expanded service by existing physicians, nurses and other allied health personnel; new and specific mechanisms that provide quality control and improved standards and decreased costs of care in hospitals; early detection of disease; implementation of the most efficient use of all phases of health care technology; and supporting the necessary catalytic role to help initiate necessary consolidation or reorganization of health care activities to achieve maximum efficiency."[1] Thus, it was a new direction, with the emphasis on health care economics in place of the legislated purposes of quality and regionalization.

Regardless of the advisability of Regional Medical Programs taking on these responsibilities (several of which were new and, many observers thought, inappropriate for RMP), even if they were to have been carried out the budget managers were willing to provide only $52.4 million in new money, about half what had been available in 1971. It became more apparent that the Administration expected Regional Medical Programs to concentrate on delivery of primary care, emergency medical services, health manpower development and cost containment, with categorical and continuing education program activities held to a minimum. In fact, the term *continuing education* was to become one not to be politely used.

The authorization for new money as proposed in the President's budget message to Congress carried with it the assumption that the carryover funds, an unprecedented $34.5 million, would

make a total of $86.9 million available for RMP fiscal 1972 activities. Yet it had been increasingly difficult as the year passed to persuade the HEW budget managers, and, later, the Office of Management and Budget, to release these carryover funds. The proposed $86.9 million funding level for all of the 56 RMP regions represented a cut of $20 million in one year. As the early months of 1971 passed, the Administration reduced RMP funding levels and it became increasingly probable (if the views of the then-Secretary of HEW Elliott Richardson and his colleagues were as pessimistic as they seemed) that the $34.5 million would not be awarded for Regional Medical Programs, but would be retained at year's end to be carried over to fiscal 1972.

Coordinators of the 56 RMP regions felt that some effort should be made directly with the Secretary's office to argue for the release of more money. Seven representatives of the RMP's, the American Medical Association, the Association of American Medical Colleges, and the Kidney Foundation met with Secretary Richardson and several of his colleagues in May. The meeting began with a decidedly negative cast, but ended with a renewed interest on the Secretary's part in the accomplishments of RMP's and an unstated pledge to seek further responsibilities for Regional Medical Programs. There was no agreement on the release of the $34.5 million, but RMP's were charged that spring with helping to define "health maintenance," to set criteria for quality in health maintenance organizations and to develop and set in motion quality control activities. It seemed to the RMP's then, if not in later perspective, that they had won their point and the Administration did not, after all, intend to phase out the program.

A $10 million supplemental appropriation for RMP's in fiscal 1971 was heavily endorsed by Congress to help restore some of the momentum lost to the programs through the Administration cutbacks, and the Administration adopted a concept of level funding for Regional Medical Programs for fiscal 1972. Toward the end of that election year, however, when it became apparent that Caspar W. Weinberger was to move from his position as Director of the Office of Management and Budget to Secretary of HEW, RMP coordinators began to feel apprehensive about the program. Their gravest concerns were realized when the President's health budget for fiscal 1974 was published, with Regional Medical Programs slated for oblivion by June 30, 1973.

Arguments were heard like drum-fire from Administration spokesmen that RMP's had been too closely linked to categorical disease activities and had not really served the needs of people (whereas an early 1973 HEW document covering the previous year showed that more than half of the 9.6 million people directly served through RMP auspices had been in primary and emergency care settings), and that RMP projects "have not been carried out according to any consistent theme or set of authorities." No one in authority bothered to add that it was because of the Administration's various mandates for change in the program's purposes and direction that "any consistent theme" failed to exist.

As Director of the OMB, Mr. Weinberger declared that (1) "It is not an appropriate use of federal funds to finance continuing education for professionals generally capable of financing their own education to improve professional competence"; (2) "Originally established to upgrade health care of persons threatened by heart disease, cancer, stroke, kidney disease and related diseases, the RMP's in recent years sought more to improve access to and generally strengthen the health care delivery system"; and (3) "Dismantling the superstructure of the RMP's will also reduce the competition for the limited staff available with the skills needed to make a contribution to improving the health service system in the U.S." He added that after an expenditure of nearly $500 million during the life of the program "there is little evidence that, on a nationwide basis, the RMP's have materially affected the health care delivery system."[2] Yet Administration spokesmen had called RMP the best link government had with health providers.

Congress was yet to be heard from but on February 1, 1973, the Administration sent telegrams to all RMP coordinators, requiring that plans for phasing out operations by mid-year be submitted by March 15. The Administration began impounding funds for a wide range of programs, many of them, including RMP, in health. The RMP's began dismantling their operational and program staffs, and many patients who had been helped by the specialized services brought into being through RMP training and demonstration projects no longer could receive the individualized

and often highly technical aid. Although RMP's nationally represented in dollars a very small part of the programs that Mr. Weinberger indicated he would cut or discontinue, he probably mentioned RMP more often than any other program in his early 1973 public discussions of the need to reduce federal spending. During this period Congressional leaders reiterated their intent to keep RMP and other health programs alive.

Congress had before it the extension of the 16 programs contained in the Public Health Service Act, the legislative authorization for which ended on June 30, 1973. It was generally agreed that many provisions of the PHS Act needed to be revised and the stratagem to renew the Act for one year in order to allow sufficient time for reflection on the revamping of the code was adopted with overwhelming support. The Administration did not favor the blanket one-year extension and Mr. Weinberger took the unusual step of lobbying Congress personally to argue against the bill; but it was passed unanimously in the Senate, by a vote of 94-0, and had an overwhelming 372-1 tally in the House of Representatives. Mr. Nixon signed the measure and it became law in late June.

Then began some additional confusions and uncertainties as various levels of the Administration argued that funds could or could not or would or would not be released before June 30. Some $6.9 million in funds was released to the regions on the last day of the fiscal year with the stipulation that they could not be spent and the remaining impounded funds were incorporated in the law suit filed against the government by the National Association of Regional Medical Programs.

The one-year extension of the Public Health Service Act had become law, but since the Administration had expected that Regional Medical Programs would expire by June 30, except for the necessary tidying up that might carry through until February 15 at the latest, there were no plans for the program once fiscal 1974 began on July 1. Consequently there were no directions for several weeks about what was expected. Three of the 56 regions were closed down because the Administration believed them to have been demonstrably inadequate. Finally, on September 7, a new mission statement was issued outlining five program areas, to which RMP's were to be restricted: quality care assurance, emergency medical services, hypertension, kidney disease and development of new and more effective manpower utilization and training programs and assistance to comprehensive health planning agencies in carrying out the provisions of Section 1122 of the Social Security Admendments of 1972. Again, this represented a significant change in the program.

As the law suit progressed, it became apparent that the RMP's had more than a good chance of winning their case. Finally on February 7, 1974, the court ordered Secretary Weinberger to pay the $126 million in impounded fiscal 1973 and 1974 funds to the nation's Regional Medical Programs. While the Administration could appeal the verdict, the court required that the orders be carried out immediately, regardless of appeal.

On the second major point in the suit, namely that the RMP's be relieved of the mandatory termination date of June 30, 1974, the court found as a "conclusion of law" that "operational activities" of RMP's "should be permitted to proceed unhindered" by HEW or the Office of Management and Budget, "and this should be done until Congress indicates a contrary intention." The conclusion apparently allows the possibility of keeping selected RMP projects operating through fiscal 1975.

In addition to the order on release of funds and a relaxation of the June 30, 1974, termination date for RMP's, the court lifted the program restrictions imposed by the HEW Secretary in the September 7, 1973, directive containing the "priorities and options" section limiting RMP activity to the five major areas. The court found that HEW may legitimately be faced with time and funding constraints because of reduced RMP activity, and that its managers must be allowed to find ways to make the program as effective as possible. "However, they must do so in a manner consistent with congressional, not self-imposed, time and budgetary limitations." In addition, the court found, "The defendant administrators may not refuse to accept applications for programs in subject areas that are within the purposes outlined by the statute." The court also ordered the defendants to "rescind in writing all directives inconsistent" with its order "and notify recipients of such directives" that they are no longer applicable. The February 7 order became effective immediately and the court ordered the government to pay the costs of the suit.

If the court order prevails and its intent is obeyed, the RMP's programmatically can return to their earlier purposes, at least until Congress

acts on any extension of the Public Health Service Act.

In a short span of time, the program's purposes have been bent and twisted from improving the quality of care to creating new care, to controlling the cost of care, and now supposedly back to the intent of the law. And those same forces which caused the twisting and turning cried the loudest about the lack of "any consistent theme."

The future for the nation's health programs is in the hands of Congress. The expiration date of June 30, 1974, for most of the Public Health Service Act is rapidly approaching and it is doubtful if there is time to revamp all of the programs before that date. Some or most will probably be extended for one more year to allow time for hearings and debate.

During early 1974 there have been moves to combine the functions of planning, regulation, improvement and implementation of care into one organization at the local level. It is to be hoped we can avoid this pitfall. Planners are not regulators by nature or training, and should not be assigned regulatory functions. What we need from planning is a plan which indicates community-health needs—that is, a graphic indication of the deficits and excesses that exist in terms of health care services. Regulation, to the extent that we have it, should give major consideration to the plan when decisions about the health care system are made. But the same people should not perform both functions if objectivity and justice are a desired result. Nor are regulators and planners the best implementers of services. Implementation requires the skills of those who have had the experience of providing service. Quality determinations should be based on provider research and experience. To mix the three functions in one staff and organization is tantamount to placing the legislative, judicial and administrative function in one unit. Equitable conclusions would be hard to achieve. RMP has proven itself to be the best implementer of services in terms of access and quality based upon provider experience. This resource should not be wasted.

REFERENCES

1. The Budget of the United States Government: Fiscal Year 1972—Appendix. Executive Office of the President, Office of Management and Budget, 1971, p 398

2. The Budget of the United States Government: Fiscal Year 1974—Appendix. Executive Office of the President, Office of Management and Budget, 1973, p 383

Special Article

Refer to: Lee PR: Medicine and public health in the People's Republic of China—Observations and reflections of a recent visitor. West J Med 120:430-437, May 1974

Medicine and Public Health in the People's Republic of China

Observations and Reflections of a Recent Visitor

PHILIP R. LEE, MD, *San Francisco*

INTEREST IN THE DEVELOPMENTS in medicine and public health in the People's Republic of China has grown rapidly since the historic visit to China in 1971 by Drs. Dimond, White, Rosen and Sidel.[1] After a lapse of almost 24 years, American physicians were welcomed to China and since that time a growing number of health professionals has been offered opportunity to visit for periods ranging from a few days to many weeks.

This report is based on my observations as a member of a United States medical delegation visiting the People's Republic of China from June 15 to July 6, 1973, as guests of the Chinese Medical Association. My own observations were supplemented by a review of some of the current literature available on developments in medicine and public health in the People's Republic of China during the past 24 years.

One question often asked of delegation members is, "Why a medical mission?" The simplest answer is, "politics." Equally important, however, is the genuine interest of Chinese and American physicians and other health professionals in reestablishing and expanding their traditional ties of friendship. Medicine and public health are excellent selections as fields for exchange because they are the most universal and nonpolitical of sciences. Such exchanges are likely to foster mutually beneficial relationships because concern about health transcends ideological and political differences. China is of particular interest to the West because of its remarkable progress in medicine and public health during the past 24 years. The Chinese are justly proud of their accomplishments, but they are also aware of Western scientific advancements from which they would like to benefit.

China is still a poor country. Poverty, by any economic measure, is widespread. Agriculture is the principal occupation and much of the farming is done, as it has been for thousands of years, by hand labor. Housing in the villages has been improved, but many people still live in mud huts or thatch-roofed, small, wooden houses. In the cities, three- to five-floor apartment buildings have replaced slums, but the living conditions are still very crowded. Sanitation in the rural areas is primitive but adequate. Modern water supply and waste treatment systems are found in all the major cities. In the industrial areas, air pollution was very evident and in some cities pollutants seemed to fill the air. Many of the health facilities we visited were old, the equipment was primitive, and most of the buildings had not had a coat of paint for years.

Before the establishment of the People's Republic of China in 1949, the health problems in China were as staggering as they were notorious. Millions of people lost their lives in repeated, widespread epidemics, aggravated by floods, droughts and famines. The high incidence of in-

Dr. Lee is Professor of Social Medicine, Department of Medicine and Health Policy Program, School of Medicine, University of California, San Francisco.

Presented to the Medical Staff Conference, School of Medicine, University of California, San Francisco, August 22, 1973.

Reprint requests to: P. R. Lee, MD, Health Policy Program, University of California, San Francisco, 1326 Third Avenue, San Francisco, CA 94143.

TABLE 1.—*Significant Developments in Medicine and Public Health in the People's Republic of China, 1949-1973*

1949	People's Republic of China founded Ministry of Public Health established
1950	Marriage Law enacted, providing equal rights for women First National Health Congress held, placing emphasis on rural health services Ministry of Public Health initiated studies of venereal disease Pharmaceutical industry nationalized
1951	Prostitution made illegal Campaign to control venereal disease in minority regions
1952	First Patriotic Health Campaigns: village water sanitation, and campaign to eliminate pests (flies, rats, mosquitoes, bed bugs) First penicillin produced
1953-57	First Five-Year Plan, placing greater emphasis on industrialization and urban health services Pharmaceutical industry expanded, particularly for production of antibiotics
1954	Central Research Institute of Dermatology and Venereology established
1955	Academy of Traditional Chinese Medicine established in Peking
1956	Agriculture and rural health services reemphasized
1958-59	Great Leap Forward, with the commune emerging as basic organizational structure for agriculture production and rural medical care system Rural health services expanded, with establishment of health centers, incorporation of traditional practitioners, transfer of urban health personnel to countryside, training of part-time auxiliary health workers
1960	Technicians from Soviet Union withdraw
1965	Mao's June 25 directive: "In health work, put stress on the rural areas" Mobile medical teams increased and moved from the cities to rural areas; one-third of all urban doctors serving in the countryside Training of "barefoot doctors"
1966-69	Great Proletarian Cultural Revolution; all medical, dental, pharmacy, nursing and public health schools closed. Minister and Vice-Minister of Public Health removed (1967)
1970-71	Medical and other health professions schools readmit students
1971	American physicians visit for the first time in 24 years
1972	President Nixon visits People's Republic of China. Decision made to open liaison offices in Washington and Peking. Exchange expands

fectious diseases, particularly gastrointestinal disease, tuberculosis, smallpox, schistosomiasis, malaria and the respiratory-diarrhea disease syndromes in infancy, caused death rates that were as high as any in the world. Sanitation was virtually unknown in the rural areas where the great majority of the people lived. Most of the scientifically trained medical personnel were in the cities and usually they limited their care to private patients who could pay their fees.

The picture today is dramatically different. One need not accept the descriptions that have appeared in official Chinese publications, although many of these have now been confirmed. In the past ten years, writers, social scientists, physicians and others visiting China have described the striking changes in the health of the people. Statistics are not readily available, but it is clear that there has been a pronounced decline in the death rate, particularly infant mortality. Major epidemic diseases have been controlled, and in some cases apparently eradicated. Nutritional status has been improved. Massive campaigns of health education and environmental sanitation have been carried out. Large numbers of health workers have been trained, and a system has been developed that provides some health service for the great majority of the people.[2-15]

It is apparent that progress has not always been smooth. Programs that were emphasized in the early 1950's were discarded in the 1960's and 1970's. Health professions schools were closed during the Cultural Revolution. Important steps were taken, however, including the establishment in 1949 of the Ministry of Health, the enactment of marriage laws providing equal rights for women, the initiation of mass health campaigns, the emphasis placed on rural health services, and the attempts to integrate traditional Chinese and Western medicine (Table 1).

Two questions are of particular interest to American physicians:

- How, in so short a time, did the Chinese manage to transform a country where the death

rate was among the highest in the world, epidemic diseases were widespread, sanitation was primitive and modern medical care was essentially limited to the urban elite, into a country where the health status of the population now ranks well ahead of that of most developing nations, most of the people have an appreciation of sanitation and the great majority have access to health care?

- Is there anything Americans can learn from the Chinese experience in medicine and public health?

Health Policies and Programs

A variety of explanations might be given for the accomplishments in medicine and public health in the People's Republic of China during the past 24 years. I believe two factors were of major importance: the priority accorded public health programs and a clear set of guiding principles.

The Communist government in China has given high priority to health from its inception. The reasons are both humanitarian and economic. A healthy person is more productive, particularly when agriculture is basic to the economy and the methods of production greatly depend on human labor. Farming in China is hard work. A disease-ravaged population simply cannot produce the food needed to feed itself, let alone food for export and development of capital for industrialization.

The four principles adopted at the First National Health Congress in 1950 have remained the basic health policies for China. These proved to be sound because they produced a large health benefit with a relatively small financial cost and they made use of China's huge untrained manpower pool. The policies have been stated in a variety of ways, but basically there are four:

- Health workers should serve primarily the masses of laboring people—peasants, workers and soldiers.
- Emphasis should be placed on disease prevention.
- Close unity should be fostered between traditional and modern doctors.
- Health work should, whenever appropriate, be conducted through mass campaigns with the active participation of medical workers.

Eighty percent of China's people live in rural areas. Chairman Mao has placed an emphasis on health care in the rural areas, where preventive measures and access to health treatment had been almost nonexistent. In the last 24 years a massive program involving millions of health workers has vastly altered health in the rural areas, where formerly half the people died before they reached the age of 30. This health program involved a massive training program and a major mobilization and organization of health services, linked with the mass campaigns.

The training of medical personnel has been as important as the organization of health services. China faced a great shortage of health manpower with very little foundation to develop programs to meet the health care needs. The approach used at first was based on the Soviet Union model and China received extensive assistance from Soviet technicians. The Soviet model separates training for prevention from training for cure; the six-year medical schools produce large numbers of specialists in both adult and pediatric illnesses. The most important development during this early period was the restructuring of the medical schools and a massive expansion in numbers of schools and students.

Also based on the Soviet model, the "middle medical school" was another innovation introduced in the 1950's and 1960's. These included training programs for feldshers, nurses, midwives, pharmacists, and radiology and laboratory technicians.

Soviet technicians began to leave China in 1960 and the shift in government emphasis was seen in the establishment of programs to train "barefoot doctors" in 1965. In that same year, Chairman Mao's major directive stated: "In health work, put stress on the rural areas." There was also at this time a rapid shift in assignment of mobile medical teams from the cities to the rural areas. It is estimated that one-third of all urban doctors were serving in the countryside.

Although the training of a variety of part-time health workers, including barefoot doctors, was initiated during this period, the program was not emphasized until the Cultural Revolution (1966-1969). Then, all medical, dental, public health, pharmacy and nursing schools were closed and emphasis was placed on service and training people on farms and in factories to meet local needs. The professional schools began to reopen in 1971, but with some pronounced changes. For example, the medical schools were now three-year programs. Students entered after the equivalent of an American junior high school education, and a

period of time working in the fields or in the factories.[16-19]

There are an estimated one million barefoot doctors in China today. Training of barefoot doctors apparently varies from one to six months, with the usual described as three to six months in duration. Training often is alternated with field experience, the trainee spending a month in a commune or county hospital, then a month with a mobile medical team, another month in a hospital, and then back in the field again. The training involves mainly simple hygiene, simple anatomy and physiology, preventive measures, immunization, diagnosis and treatment of common conditions, treatment of respiratory infection and treatment of diarrheal disease. More complicated problems and surgical cases apparently are referred to the commune hospital. Barefoot doctors treat their patients with antibiotics and other medications.[20-22]

In China's preventive medicine program, stress has been placed on environmental sanitation, health education, immunization, maternal and child health and the control of communicable diseases. The results have been impressive by any standard.

Following the advice of Soviet technical advisors, one of the first steps was establishing epidemic control and prevention centers throughout the country. These centers were charged with responsibility for health education and immunization. They also were often involved in organizing and training workers for campaigns to control specific diseases. Medical teams from these centers traveled to the villages to explain to peasants all facets of personal hygiene and environmental sanitation, ranging from why they should wash their hands to how communal latrines should be built. Maternal and child care centers were established and they provided not only obstetric and pediatric services, but also education for mothers on the general health and hygiene of the household.

Between the periodic intensive campaigns there were constant preventive reminders via lectures, posters, newspapers, radios and small-group discussions. The resulting social pressures were probably more responsible than any other activity for changing the attitudes and behavior of the Chinese people toward hygiene. All these programs were carried out at a relatively small cost to the central government and despite serious shortages of trained medical personnel.

A major feature of the public health program is the mass patriotic health campaigns which have been carried out periodically since the early 1950's. The mass inoculation and clean-up campaigns depend more on efficient organization and widespread propaganda (or publicity) than on large expenditures of money and highly trained personnel.

One of the first of these campaigns was launched to eliminate the four pests: rats, flies, mosquitoes and bed bugs. A visitor to China today is impressed in rural and urban areas alike with the success of this effort. The program to control or eliminate venereal disease was another successful mass health campaign. A key architect of this program is Dr. Ma Hai-teh (George Hatem), an American-born, Swiss-trained physician who has worked in China since the mid 1930's. The program was made possible by a variety of developments, not the least of which was the ability of the Chinese to mass-produce penicillin. Equally important were social and economic changes, including legislation enacted in 1950 providing equal rights for women, and later legislation outlawing prostitution. It was also necessary to detect those with syphilis and gonorrhea, using low-cost methods that the people would accept. This was not an easy task and it could not be accomplished by Western approaches such as blood tests for large numbers of the population, because trained manpower and money were not available.

Dr. Ma Hai-teh discussed the campaign during an automobile trip from Peking to the Great Wall. His description followed the details of his article on the subject, which appeared in *China's Medicine*.[23] He explained that an essential element of the program was "the eradication of the social and economic causes of venereal disease." This involved the legislation eliminating prostitution and providing for equal rights for women. The mass public health campaign included developing methods for and training a cadre for venereal disease detection and treatment, including consistent follow-up efforts, as well as a mass propaganda campaign.

In his article and in his discussion with me, Dr. Ma Hai-teh emphasized the role of the masses in the campaign and the importance of political factors in making the effort a success. Gonorrhea and syphilis are now unknown in China.

The Organization and Financing of Health Services

The Ministry of Health is the central health body at the national level. Health departments or bureaus exist in each of the 22 provinces, five autonomous regions and three municipalities that are the equivalent of provinces (Shanghai, Peking and Tientsin). Most municipalities include the following administrative units: districts, streets (neighborhoods) and lanes. In the rural areas, the communes are organized on the basis of production brigades and work teams. Each production brigade has a medical unit which includes barefoot doctors and other health workers. There are 2,200 counties and over 70,000 communes in China. More than 550 million people live in the rural areas and as many as 200 million live in the cities.

Health planning is centralized in the provincial and national governments, but programs are decentralized, with most services provided at the local level. Medical research is carried out under the Academy of Medical Sciences of the Ministry of Health. The academy operates some hospitals and medical schools but medical education is primarily a function of the provincial governments which also operate public health programs and hospitals. These hospitals are referral centers and are used to train health workers at various levels. The counties also maintain hospitals and health centers.

The figures on communes are not clear but probably 70 percent have some form of cooperative medical care system with a hospital or health center as the central facility. Our medical delegation visited three communes with populations ranging from 27,500 to 78,000. Each has a central hospital and health center. We also visited production brigade (village) health stations which are primitively equipped facilities run by barefoot doctors. Midwives and other part-time health workers also work out of these stations. The facilities we observed are apparently fairly typical of communes throughout China.

All of the institutions we visited—hospitals, medical schools, communes and factories—are governed by revolutionary committees, each consisting of representatives of the People's Liberation Army, the cadres (party workers and administrators) and the masses. In a hospital, the masses would include doctors, nurses and other health workers. The revolutionary committees function as the principal policy and management bodies of their institutions.

Health services are financed by a combination of general tax revenues, health insurance funds, and private funds, the latter paid on a fee-for-service basis.

It is of interest that the People's Liberation Army has its own health service for members of the armed forces. In addition to this cost, the central government pays the entire cost of health care for administrators, public servants, students and others whose work is defined as serving the national interest. It also subsidizes the production and distribution of drugs and medical appliances. The national, provincial, municipal and county governments pay for the construction of health care facilities and for the purchase of equipment. The national or provincial governments pay one-half of the cost of building hospitals, health centers and other facilities in communes and at the district, lane and street levels in the cities. The national and provincial governments pay for medical education and a variety of public health programs, including family planning. Oral contraceptives, for example, are provided without charge.

Health care for factory workers, miners and others in state-operated industries, is financed by the state. The cost is borne as part of the cost of production and the worker pays nothing. Families of factory workers are subsidized for one-half of the cost of their care; the rest is paid out-of-pocket on a fee-for-service basis.

In the rural communes, a cooperative medical service system has been established which is financed almost entirely by the peasants. Each commune's health service is financed on a capitation, prepayment basis. The cost is low, about 20 cents (U.S.) per person per month. If the patient must go to a county or provincial hospital for care and the cost of the illness is high, the commune welfare fund helps pay the cost. The county or provincial hospital may also subsidize the cost of treatment.

Health Services in Rural Areas—Meeting the Needs of the People

The government has taken a number of steps to increase the availability of health services in the rural areas:

- Medical workers have been encouraged to settle in the rural areas. Since 1949, more than

130,000 doctors and other medical workers have resettled in the countryside.

- About 170,000 new graduates of medical colleges and medical schools have been sent to the countryside to work.
- Mobile medical teams have been organized and around 700,000 members have gone to the villages to deliver medical care.
- Barefoot doctors and other part-time health workers have been trained to provide some primary medical services, including immunizations and other preventive services, and to educate the people on matters of environmental sanitation and family planning. More than one million barefoot doctors and more than three million additional part-time health workers have been trained.
- Drugs have been made easily available at low cost.
- The use of traditional medicines is being explored and expanded. More than 140 small workshops have been set up in rural areas throughout the country to make use of medicinal herbs. Some of these plants grow naturally and others are cultivated in communes. There are perhaps 3,000 traditional medicines available and over 800 in common use for the treatment of myriad diseases.

The mobile medical teams have played an important role in the delivery of health care in the rural areas and in the training of barefoot doctors and other health workers. In his book, *Away With All Pests,*[24] Dr. Joshua Horn, a British physician who spent 15 years in China, describes the work of these teams and classifies their major tasks:

- Provide preventive and therapeutic services, with preventive work given priority;
- Train auxiliary medical workers from among the local people;
- Make the Party's planned parenthood policy become a reality;
- Cooperate with and raise the level of local medical services; and
- Cooperate with and assist the patriotic health campaigns.

Members of the medical teams are urged to use the opportunity of a year in the countryside to deepen their understanding of the laboring people, so that they will fit better into the new society and become more effective in building socialism. This ideological remodeling of the medical team members is the key to the program's goals, according to Dr. Horn.

At the Malu commune outside Shanghai, the American delegation met members of a mobile medical team from Shanghai. The vice-chairman of the commune revolutionary committee described the evolution of health services in the commune, the mass campaign against smallpox, cholera and schistosomiasis, the training of barefoot doctors and the introduction of the cooperative medical service after the Cultural Revolution. In all of these activities, the Shanghai mobile medical teams have played an important role. The vice chairman of the revolutionary committee stressed, however, that the most important role was played by the people of the villages in the mass campaign and other programs of prevention.

The stress on prevention was particularly evident in the communes, including the hospitals, health centers and health stations. The barefoot doctors are involved in programs of environmental sanitation, immunization, well-baby care and family planning as well as diagnosis and treatment.

Fostering Unity Between Traditional Chinese Medicine and Western Medicine

A key factor in the campaign to meet the health needs of the hundreds of millions of Chinese, especially those in the rural areas, is the policy of integrating traditional Chinese medicine and Western medicine. This decision was a practical one. First, many of the nation's leaders apparently had faith in the benefits of traditional Chinese medicine. Second, the great majority of the people had never been exposed to any other kind of medicine. Finally, to provide physicians trained in Western medicine for a rapidly growing population of over 500 million people in the early 1950's, would have taken generations and a huge investment of scarce resources. Therefore, the policy to foster close unity between traditional Chinese medicine and Western medicine was established by the First National Health Congress in 1950. The policy was not consistently honored by the leaders in medicine who had been trained in the Western scientific tradition. Their attitudes began to change, however, with the demonstration of the value of acupuncture anesthesia. The policy received even greater emphasis during the Cultural Revolution.

Western visitors, particularly physicians, receive heavy exposure to the techniques of traditional Chinese medicine, such as acupuncture and herbal remedies. During the course of our trip we saw surgical procedures performed with acupuncture anesthesia in national, provincial and muni-

cipal hospitals. Most of these are teaching hospitals affiliated with medical schools. In most commune hospitals, however, spinal, epidural and local anesthesia are more common. Dr. John Bonica, Professor and Chairman of the Department of Anesthesiology, University of Washington, made a brief survey during our three-week visit and found that in the hospitals we visited, acupuncture anesthesia was used for 5 percent or less of the surgical procedures in commune hospitals, for 10 percent of the surgical cases in the four factory or municipal hospitals, and for 15 to 20 percent of the operations in five medical college or Academy of Medical Sciences affiliated hospitals. There is no doubt that for certain types of procedures, such as thyroidectomy, it is the anesthesia of choice. It is being used for thoracotomy, laparotomy and various intra-abdominal procedures, as well as for craniotomy and some orthopedic procedures.

The techniques of acupuncture anesthesia vary from one hospital to another for the same operative procedure. There is even some variation evident within a given hospital. There does not appear to be a standard technique for any specific operation.

The action mechanisms of acupuncture are under investigation, particularly at the Institute of Physiology, Chinese Academy of Sciences, Shanghai. The experiments are well conceived and executed but research equipment and techniques are far behind those of the United States, England and other countries engaged in neurophysiological research. We saw little evidence that clinical research was being done on the effects of acupuncture.

In addition to anesthesia, acupuncture is widely used for a variety of medical conditions. Such treatments have traditions dating back thousands of years. It is possible that acupuncture is a therapeutic means of broad or limited clinical usefulness, acting through as yet unknown mechanisms. Only time and careful clinical trials will give the answers.

The beneficial effects of herbal remedies and other traditional medicines were repeatedly emphasized by the Chinese practitioners we met. At the Fu Wai Hospital in Peking, we were shown clinical trials of an herbal remedy that was felt to be useful in the treatment of angina pectoris. This hospital is operated by the Cardiovascular Research Institute of the Chinese Academy of Medical Sciences. At the Institute of Materia Medica we observed similar demonstrations of the laboratory studies relating to the extraction of active ingredients from herbal remedies, chemical synthesis and later clinical trials. At the Traditional Medical School we saw a combination of Western and traditional methods used in the treatment of a fracture of the humerus.

In every hospital, health center and dispensary we visited, the pharmacies contained both Western and traditional remedies. There were drawers and boxes with leaves, herbs, sea shells, dried-up bones, seeds, roots and snake skins. Nearby would be vials or bottles of penicillin, chloramphenicol, phenobarbital, meprobamate, cortisone, liver extract, vitamin B-complex and a wide variety of other modern medicines—all made in the People's Republic of China.

I was far more impressed by the developments in pharmaceutical manufacturing, drug distribution and use than I was in the attempts to find effective remedies among the thousands of traditional Chinese medicines now in use. Based on our observations and those of others, I would agree with the recent observation of Dr. James Y. P. Chen, a long-time student of the People's Republic of China: "Following 20 years of perseverance and self reliance, the pharmaceutical industry has changed from an industry reprocessing imported drugs to a completely self-sufficient manufacturing organization."[25]

Particularly impressive is the availability of modern antimicrobial drugs, including penicillin, chloramphenicol, tetracycline, dihydrostreptomycin, isoniazid and nitrofurans which are widely available in hospitals, health stations and neighborhood drugstores without prescription. These agents are also frequently prescribed by barefoot doctors and physicians for minor respiratory infections and diarrhea and their over-use appears to present problems very much the same as those in the United States.

The use of oral contraceptives, by contrast, appears to be rational and simple. Prescribed by barefoot doctors as well as physicians, the procedures for prescribing and for follow-up of patients appear to be standardized and well controlled. Oral contraceptives are prescribed only for married women, and, unlike antibiotics, are not available over the counter.[26,27]

Research and development related to antimicrobial drugs appears to be active. Investigation

of new drugs is under the direction of the Academy of Medical Sciences, particularly the Institute of Materia Medica. Research is also done in the medical colleges and the Institute of Organic Chemistry in Shanghai, one of the research institutes of the Academy of Sciences.

Summary

Remarkable advances in medicine and public health have taken place in the People's Republic of China during the last 24 years. Basic to the improved health of the Chinese people during this period is the emphasis on public health programs and the guiding policies that were established by the First National Health Congress in 1950. In my opinion the most significant accomplishments have been the development of a network of rural health services; the training of large numbers of health workers; the deployment of trained medical professionals from the urban to the rural areas; the curtailment of communicable diseases through mass campaigns; improved nutrition and environmental sanitation; the development of a modern pharmaceutical industry, making possible the widespread availability of antimicrobial agents and effective oral contraceptives; and, more recently, the priority given family planning programs.

REFERENCES

1. Dimond EG: More than herbs and acupuncture. Saturday Review 54:17, Sep 18, 1971

2. Dimond EG: Medicine in the People's Republic of China. JAMA 222:1158-1159, Nov 27, 1972

3. Stanley M: China then and now. Am Jour Nursing 72:2213-2218, Dec 1972

4. Rifkin SB, Kaplinsky R: Health Strategy and Development Planning. Lessons from the People's Republic of China. J Developmental Studies 9:213-232, Jan 1973

5. Ling MH, Eichling PS, Fine LJ, et al: Chinese health care: Determinants of the system. Am J Public Health 63:102-110, Feb 1973

6. Cheng TO: A view of modern Chinese medicine—Observations by a Shanghai-born physician during his recent visit after 22 years absence. Ann Int Med 78:285-290, 1973

7. Woodley J: A doctor's journey into China. Eastern Horizon 12:7-27, 1973

8. Huang Shu-tse: Development of national public health services. Peking Review 16:5-7, May 25, 1973

9. Geiger HJ: Putting China's medicine in perspective. Medical World News 14:43-49, May 18, 1973

10. Geiger HJ: A pragmatic approach to medicine (China, Part 2). Medical World News 14:22-30, Jun 1, 1973

11. deHaas JH, deHaas-Posthuma JH: Sociomedical achievements in the People's Republic of China. Int J Health Services 3: 275-294, 1973

12. Quinn JR: Medicine and Public Health in the People's Republic of China. Washington, D.C., Department of Health, Education, and Welfare, 1973, p 333

13. Sidel VW: Some observations on the health services in the People's Republic of China. Int J Health Services 2:385-395, Nov 1972

14. Horn JS: Building a rural health service in the People's Republic of China. Int J Health Services 2:377-383, Nov 1972

15. Lampton DM: Public health and politics in China's past two decades. Health Service Reports 87:895-904, Dec 1972

16. Orleans LA: Medical education and manpower in Communist China. Comp Educ Rev:20-42, Feb 1969

17. Dimond EG: Medical education and medical care in the People's Republic of China. JAMA 218:1552-1557, Dec 6, 1971

18. Chan Chi-chao: Medical education in Mainland China. J Med Educ 47:327-332, May 1972

19. Berger R: Medical training in China. Eastern Horizon 12: 28-36, 1973

20. Pickowicz PG: Barefoot doctors in China: People, politics, and paramedicine. Eastern Horizon 11:25-38, 1972

21. Sidel VW: The barefoot doctors of the People's Republic of China. N Engl J Med 286:1292-1300, Jun 15, 1972

22. Barefoot doctors—Giving medical treatment while taking part in farm work. Peking Rev 16:15, May 25, 1973

23. Ma Hai-teh (George Hatem): With Mao Tse-Tung's thought as the compass for action in the control of venereal disease in China. Chinese Med 1:52-68, October 1966

24. Horn JS: Away with All Pests, New York Monthly Review Press, 1969, p 192

25. Chen JYP: Pharmacology, *In* Quinn JR: Medicine and public health in the People's Republic of China. Washington, D.C., Department of Health, Education, and Welfare, 1973, pp 93-110

26. Orleans LA: Every Fifth Child—The Population of China. Stanford, California, The Stanford University Press, 1972

27. Aird JS: Population Policy and Demographic Prospects in the People's Republic of China. Washington, D.C., Department of Health, Education, and Welfare, 1972

Refer to: Access to medical care as a citizen's right (California Medical Association Position Paper). West J Med 120:438-439, May 1974

Access to Medical Care as a Citizen's Right

IN THIS COUNTRY, at this time, access to medical care is no longer considered a privilege, but a right. It is in the interests of our profession that we now declare our dedication to this principle. As individuals, we seek the individual health of our patients. As a profession, we seek the health of all.

Each citizen has a right to access to adequate medical care. The right to health itself, however, cannot be guaranteed, because the achievement of full physical and mental well-being is an individual responsibility. The opportunity to achieve good health through adequate medical services, however, can and should be guaranteed.

The citizen's right of access to health care is a fundamental principle of justice. Our society now

---

Refer to: Practical criteria for the diagnosis of alcoholism in hospital practice (California Medical Association Position Paper). West J Med 120:438-439, May 1974

Practical Criteria for the Diagnosis of Alcoholism in Hospital Practice

ALCOHOLISM, WHEN PRESENT, should be diagnosed as is any other disease. But the diagnosis of alcoholism for medical purposes is difficult. General agreement on the definition of alcoholism itself has been lacking. The clinical signs and subtleties of the disease are varied, elusive and without reliable parameters. Much depends on the experience, motivation and bias of the observer in deciding whether a patient has alcoholism or not.

Therefore, the establishment of workable criteria for the diagnosis of alcoholism, especially as it appears in hospital practice, would be useful in many ways. With this paper, the California Medical Association has attempted to set down guidelines in the form of gross criteria for the use of medical audit committees as they develop audit criteria for use in their own hospitals. The criteria listed here are extreme; they imply that the diagnosis of alcoholism is not only appropriate but mandatory in these situations.

The Diagnosis of Alcoholism Is Appropriate under Any One of the Following Conditions:

A. Physiological conditions—when the use of alcohol results in high tolerance and the production of withdrawal symptoms upon cessation of drinking
   1. tolerance levels
      (a) blood level of 150 mg per 100 ml without apparent intoxication
      (b) if the history shows regular ingestion of
         one-fifth distilled spirits
         two quarts fortified wine
         three quarts table wine
         twenty-three 12-ounce bottles of beer
         } *in one day for 180-pound person*
   2. withdrawal syndrome
      (a) gross tremor, hallucinations, seizures, delirium tremens

has the resources to provide medical care to all its citizens; it is therefore our moral responsibility to assure that everyone has access to those services.

To say that a right exists, however, is not to authorize any specific system to provide that right. "Consequent rights" are those that derive from fundamental rights. They are the practical means, usually in the form of legislation, through which fundamental rights are implemented. IT IS THE RIGHT OF EVERY PERSON TO HAVE THE OPPORTUNITY TO ACHIEVE AND ENJOY GOOD HEALTH AND TO HAVE ACCESS TO ADEQUATE MEDICAL CARE.

The means by which medical care is provided is a concrete, practical question which does not belong in a statement of principle about the right to care. Furthermore, any system which implements the right to care must not infringe upon the rights of those who provide that care. That system must include safeguards of the rights of physicians and other providers of care. Physicians as a group may be called upon to participate in a system which brings medical care to the people. Physicians as individuals, however, may not be required to provide a specific service at a given time or place.

This position paper was endorsed by the California Medical Association's 1974 House of Delegates. The basic statement was drafted by the CMA Committee on the Role of Medicine in Society in response to a request from the 1973 House of Delegates to prepare an accurate definition of the "health care right" (Substitute Resolution 181-73). The Committee's report was approved by the CMA Council and subsequently accepted by the House of Delegates with minor modifications.

---

3. Clinical conditions—when the use of alcohol results in diagnosable alcohol-related organ damage *and continues in spite of contrary medical advice*
   1. fatty liver
   2. alcoholic hepatitis and/or Laennec's cirrhosis
   3. pancreatitis without cholelithiasis
   4. chronic gastritis
   5. alcoholic cerebellar degeneration
   6. Wernicke-Korsakoff syndrome
   7. peripheral neuropathy
   8. alcoholic cardiomyopathy
   9. alcoholic myopathy
   10. other organ damage related to alcohol use, including accidents

C. Behavioral conditions
   1. when the use of alcohol in any amount regularly results in uncontrolled or prolonged drinking, acute psychotic reactions, or amnesia ("blackout periods")
   2. when constant and repetitive use of alcohol results in recognizable sociologic or psychological disruption
      (a) marital disharmony
      (b) job performance impairment
      (c) frequent arrests
      (d) repeated accidents
      (e) skid row behavior, that is, homelessness, joblessness, geographic isolation
   3. when the use of alcohol becomes so intertwined with a psychiatric illness that effective psychotherapy cannot proceed

Whenever alcoholism is diagnosed, it should be recorded concurrently with other diagnoses, including psychological. Regular recording of diagnoses in these obvious cases will facilitate medical audit procedures and will help to identify the elements of appropriate care—which should include after-care. Making appropriate referrals to after-care and confronting the patient with the responsibility for cooperating in therapy should become identified as necessary elements in treatment.

Charting the diagnosis on a regular basis could provide basic data necessary for standardizing third party coverage.

These benefits should help us to overcome the reluctance to document the diagnosis of alcoholism.

Approved by the California Medical Association Committee on Alcoholism and Other Drug Dependence, December 5, 1973.
Approved by the California Medical Association Executive Committee of the Scientific Board, December 12, 1973, with the endorsement of the Advisory Panels on Psychiatry and Internal Medicine.
Approved by the California Medical Association Council, January 18, 1974.
Resolution No. 152-74 accepted by the California Medical Association House of Delegates, March 6, 1974.
Reference is also made to American Medical Association Resolution 30 (C-73).

NOTE: The California Medical Association Committee on Alcoholism and Other Drug Dependence is indebted to the National Council on Alcoholism, especially its Criteria Committee and its Medical Director, Frank Seixas, MD, for the development and publication in 1972 of criteria for the diagnosis of alcoholism.

in memoriam

Erickson, Elenore J., Berkeley. Died February 25, 1974 in Berkeley of arteriosclerosis, aged 71. Graduate of the University of California Medical School, Berkeley-San Francisco, 1938. Licensed in California in 1938. Doctor Erickson was a retired member of the Alameda-Contra Costa Medical Association and the California Medical Association, and an associate member of the American Medical Association.

Fiscus, William Patrick, San Francisco. Died February 27, 1974 in San Bruno, aged 34. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1965. Licensed in California in 1967. Doctor Fiscus was a member of the San Francisco Medical Society.

Fraser, Alexander Falconer, San Francisco. Died March 9, 1974 in Daly City, aged 74. Graduate of Northwestern University Medical School, Chicago, 1935. Licensed in California in 1936. Doctor Fraser was a member of the San Francisco Medical Society.

Friedman, Henry Tauber, Beverly Hills. Died January 22, 1974 of cancer, aged 59. Graduate of Washington University School of Medicine, St. Louis, 1940. Licensed in California in 1945. Doctor Friedman was a member of the Los Angeles County Medical Association.

Gaspard, Frederic Joseph, Los Angeles. Died March 19, 1974 in Los Angeles, aged 83. Graduate of Eclectic Medical College, Cincinnati, 1922. Licensed in California in 1922. Doctor Gaspard was a member of the Los Angeles County Medical Association.

Gonzalez, Luis Guerrero, San Francisco. Died November 3, 1973 of cardiorespiratory failure and hepatic failure, aged 65. Graduate of Facultad de Medicina de la Universidad de Guadalajara, Guadalajara, Mexico, 1938. Licensed in California in 1949. Doctor Gonzalez was a member of the San Francisco Medical Society.

Greig, Kennett A., Oakland. Died February 25, 1974 in Oakland of corpulmonale, aged 59. Graduate of the University of Rochester School of Medicine and Dentistry, 1941. Licensed in California in 1944. Doctor Greig was a member of the Alameda-Contra Costa Medical Association.

Hedberg, Caleb Clifford, San Francisco. Died March 15, 1974 in San Francisco of heart disease, aged 76. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1922. Licensed in California in 1922. Doctor Hedberg was a member of the San Francisco Medical Society.

Kaye, Van Walter, Riverside. Died March 2, 1974 in Riverside of heart disease, aged 74. Graduate of Loyola University School of Medicine, Chicago, 1932. Licensed in California in 1954. Doctor Kaye was a member of the Riverside County Medical Association.

Keller, Florence, Glendale. Died January 15, 1974 in Glendale of bronchopneumonia, aged 98. Graduate of American Medical Missionary College, Chicago, 1900. Licensed in California in 1917. Doctor Keller was a member of the Los Angeles County Medical Association.

Libby, Robert Green, Oakland. Died February 25, 1974 in Lafayette of brain tumor, aged 67. Graduate of Northwestern University Medical School, Chicago, 1935. Licensed in California in 1935. Doctor Libby was a member of the Alameda-Contra Costa Medical Association.

Martin, Charles George, Chino. Died February 8, 1974 in Chino of heart disease, aged 56. Graduate of the College of Osteopathic Medicine, Des Moines, 1950. Licensed in California in 1962. M.D. degree from California College of Medicine, 1962. Doctor Martin was a member of the San Bernardino County Medical Society.

Matt, Wayland P., Bakersfield. Died February 28, 1974 in Bakersfield of heart disease, aged 58. Graduate of Loyola University School of Medicine, Chicago, 1941. Licensed in California in 1943. Doctor Matt was a member of the Kern County Medical Society.

Quickert, Marvin H., San Jose. Died March 23, 1974 while scuba diving near Santa Cruz, aged 45. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1953. Licensed in California in 1954. Doctor Quickert was a member of the Santa Clara County Medical Society.

Reamer, William Leslie, Fresno. Died January 23, 1974, aged 49. Graduate of the University of Michigan Medical School, Ann Arbor, 1956. Licensed in California in 1960. Doctor Reamer was a member of the Fresno County Medical Society.

Townsend, Ernest Witt, Los Angeles. Died February 18, 1974 in Los Angeles of myocardial infarction, aged 75. Graduate of Tulane University School of Medicine, New Orleans, 1922. Licensed in California in 1924. Doctor Townsend was a member of the Los Angeles County Medical Association.

Wagner, Claude F., Long Beach. Died February 21, 1974 in Long Beach of intestinal obstruction, aged 63. Graduate of State University of Iowa College of Medicine, Iowa City, 1939. Licensed in California in 1946. Doctor Wagner was a member of the Los Angeles County Medical Association.

Wilbur, Blake C., Palo Alto. Died March 10, 1974 of heart disease, aged 72. Graduate of Harvard Medical School, Boston, 1925. Licensed in California in 1928. Doctor Wilbur was a member of the Santa Clara County Medical Society.

Wilson, Ethelbert R., Red Bluff. Died March 20, 1974 in Red Bluff, aged 73. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1927. Licensed in California in 1943. Doctor Wilson was a member of the Tehama County Medical Society.

Yumibe, Toshio, Bakersfield. Drowned when he was swept to sea near Oceano on February 3, 1974, aged 47. Graduate of the University of Minnesota Medical School, Minneapolis, 1954. Licensed in California in 1955. Doctor Yumibe was a member of the Kern County Medical Society.

HERE Pleural effusion

Wherever it hurts, Empirin Compound with Codeine usually provides the relief needed.

HERE Biliary calculi

n general, only pain so severe hat it requires morphine is eyond the scope of mpirin Compound with Codeine.

prescribing convenience: up to 5 refills in 6 months, t your discretion (unless estricted by state law); by elephone order in many states.

mpirin Compound with odeine **No. 3,** codeine hosphate* 32.4 mg. (gr. ½); **lo. 4,** codeine phosphate* 4.8 mg. (gr. 1). *Warning— ay be habit-forming. Each blet also contains: aspirin r. 3½, phenacetin gr. 2½, affeine gr. ½.

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

WHEREVER IT HURTS

EMPIRIN® COMPOUND c̄ CODEINE

#3, codeine phosphate* (32.4 mg.) gr. ½
#4, codeine phosphate* (64.8 mg.) gr. 1

Classified Advertisements

The rate for each insertion is **$2.50 per line** (average six words per line) **with five line minimum.**

Box number charge: $1.50 each month.

Classified display rates $25.00 per inch.

Copy for classified advertisements should be received not later than **the fifth of the month preceding issue.** • Classified advertisers using Box Numbers forbid the disclosure of their identity. Your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the rules of the Advertising Committee.

CLASSIFIED ADVERTISEMENTS ARE PAYABLE IN ADVANCE

PHYSICIANS WANTED

INTERNIST, GENERALIST AND UROLOGIST, State Veterans Home and Hospital. Salary depending upon training, experience and position to be filled. Excellent retirement plan and other benefits. Located one hour from San Francisco in beautiful Napa Valley. Call or write John P. Preston, Administrator, Phone (707) 944-2422.

LOS ANGELES—ORANGE COUNTIES. Growing HMO needs more General Practitioners, Pediatricians, Orthopods, OB/GYN's and Internist. Competitive salaries, regular increases and tax-sheltered fringe benefits. Two newly opened medical centers. Send your curriculum vitae to: Frank Eaton, MD, Medical Director, Family Health Program, Room 5419, 2925 Palo Verde, Long Beach, CA 90815.

WANTED FOR COMPREHENSIVE SIX-MAN expanding medical care corporation—Family Practitioner and Internist. Small, friendly city with big-city advantages; two colleges, close to Los Angeles, San Francisco, Las Vegas, ocean, mountains. All sports, four-day week, every seventh week-end on call. Good salary first year. Permanent corporation membership after first year. Write to M. E. Baurer, MD, Manor Medical Group, Inc., 223 China Grade Loop, Bakersfield, CA 93308.

PROGRESSIVE RURAL GROUP PRACTICE—Located in the Salinas Valley near MONTEREY and CARMEL has an immediate need for two Family Practitioners and an Internist (Generalist) to join an established 9-man group practice, plus 11 consultants, incorporated in 1970. Competitive starting salary and top fringe benefits. Brochure by return mail. Please call or send C.V. to: DUANE F. HYDE, MD, Southern Monterey County Medical Group (A Professional Corporation), 210 Canal St., King City, CA 93930, Tel. (408) 385-5471.

RESIDENCIES & INTERNSHIPS—BAKERSFIELD, KERN COUNTY: Accepting applications for 1975-76. First year residencies in fully approved four year clinically oriented program (non pyramid). Applicants requiring one or more years of General Surgery for sub-specialty welcome. Full patient responsibility, supervision by full-time Board Certified General and Thoracic Chairman and Associate Director, with full-time Board Certified Neurosurgeon, Urologist and Anesthesiologist. Board Certified attending staff in plastic and ortho surgery. Salary $13,080 annually; meals. Must be eligible for California license. Contact: Chairman, Department of Surgery, Kern General Hospital, 1830 Flower Street, 93305. Phone (805) 323-7651, ext. 214.

FAMILY PRACTICE DOCTOR to join two doctor family practice group — four-day week, four weeks vacation plus two weeks for postgraduate studies. Suburban area near Rose Bowl-California. Prefer board or board eligible family practitioner. $3.250 per month to start and partnership after one year. Near three major hospitals. Both doctors teaching S.C. and Loma Linda Medical Schools; (213) 790-1103.

PHYSICIANS WANTED

SURGEON—Staff position available for Board qualified or certified General Surgeon interested in teaching and resident and intern supervision in four year fully approved clinically oriented general surgical residency program. Active teaching program centered around 350 bed county hospital with full-time Board Certified General and Thoracic Cardiovascular surgeon as Chairman of Department of Surgery and full-time Board Certified General Surgeon as Associate Director. Active services also include neurosurgery, orthopaedics, urology and plastic surgery under the direction of Board Certified specialists. Salary $32,500 annually. Must be eligible for California license. Now accepting applications for 1974-75. Contact John D. Watts, MD, Associate Director, Department of Surgery, Kern General Hospital, 1830 Flower, Bakersfield, CA (805) 323-7651.

PSYCHIATRISTS AND GENERAL PHYSICIANS—Immediate employment in modern mental hospital fifty miles north of Los Angeles. Pleasant surroundings. Salaries from $23,484 to $31,488. Contact Robert E. Moebius, MD, Chief of Professional Education, Camarillo State Hospital, Box A, Camarillo, CA 93010. (805) 482-4671, extension 2893.

PSYCHIATRISTS, GP'S for geriatric program within State hospital 50 miles north of Los Angeles. Fine climate near beaches. Salary $23,484 to $31,488. Optional monthly OD 5% extra. Other fringe benefits. Contact: Martin Gish, MD, Program Director (6G), Box A, Camarillo, CA 93010. Telephone (805) 482-4671, ext. 2638.

PHYSICAL MEDICINE REHABILITATION RESIDENCY. One opening available to join total group of seven (7) residents; approved 3 year program; UCLA affiliation. Comprehensive teaching program with four (4) Board Certified Physiatrists—includes Electromyography. Stipend 1st year $15,394 - $18,720 3rd year. U.S. licensure required. Contact Karl H. Haase, MD, Chief, Rehabilitation Medicine Service, VA Wadsworth Hospital Center, Los Angeles, CA 90073; (213) 478-3711, ext. 5210. Equal opportunity employer.

CHIEF PUBLIC HEALTH MEDICAL OFFICER—Immediate vacancy for physician who possesses California license and Master's degree in Public Health plus 3 years experience in public health agency including 1 year as director of major organizational unit of a health agency. Reports directly to the Director of Public Health and plans, organizes, directs and evaluates the programs of the Disease Control Division. Start: $2,243 or higher with step increases to $2,727 per month. Send résumé to: Stephen N. Rosenberg, MD, MPH, Director of Public Health, 351 N. Mt. View Ave., San Bernardino, CA 92415 or call (714) 383-1042.

PULMONARY MEDICINE—Internist wanted to join cardio-pulmonary group in Southern California. Finest smog-free coastal community. Excellent place to live and practice. Live within walking distance of office and hospital. Write P.O. Box 3197, Ventura, CA 93003.

SANTA BARBARA, CALIFORNIA. Ideal coastal community. Expanding medical staff at County-operated teaching hospital has openings for full-time physicians in Family Practice, Ob-Gyn, and Anesthesiology. Competitive salary and fringe benefits. Contact: Edgar Rosen, MD, Medical Director, Santa Barbara General Hospital, 300 San Antonio Road, P.O. Box 3650, Santa Barbara, CA 93105. Phone (805) 967-2311.

SITUATIONS WANTED

GENERAL SURGEON, age 58, wants to relocate in Southern California. Willing to do ER work, general practice and general surgery. Author of textbook and 100 publications. Write Box 9378, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

BOARD CERTIFIED RADIOLOGIST, well experienced in diagnosis, including angiography and isotopes. now on staff of large well known private hospital, as well as on clinical faculty of University, wishes to relocate. Interested in hospital or group practice, WILLING TO INVEST. Box 9382, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

(Continued on Page 33)

REGIONAL MEDICAL DIRECTOR

. . . for a major international corporation. The location of this assignment is on the West Coast and requires at least five years experience. Reports to the Corporate Medical Director and corporate officers, operating heads, and managers within the assigned area of the West Coast. Involves contact with corporate medical installation, industrial relations departments, accident prevention units, and local health facilities embracing clinics, general hospitals, alcoholic treatment centers, and veterans' and governmental hospitals. Attractive salary and benefit program. Send complete résumé in confidence to Box 9383, Western Journal of Medicine, 731 Market St., San Francisco CA 94103.

An Equal Opportunity Employer M/F

COMPTON FOUNDATION HOSPITAL

820 West Compton Boulevard
COMPTON, CALIFORNIA 90220
(213) 537-3070
(213) 631-1148

G. CRESWELL BURNS, M.D.
Administrator and Medical Director

HELEN RISLOW BURNS, M.D.
Assistant Medical Director

MEMBER OF
American Hospital Association
and
National Association of Private Psychiatric Hospitals

High Standards of Psychiatric Treatment . . . Serving the Los Angeles Area

☆

Accredited by Joint Commission on Accreditation of Hospitals

Spasm reactor?

Donnatal®!

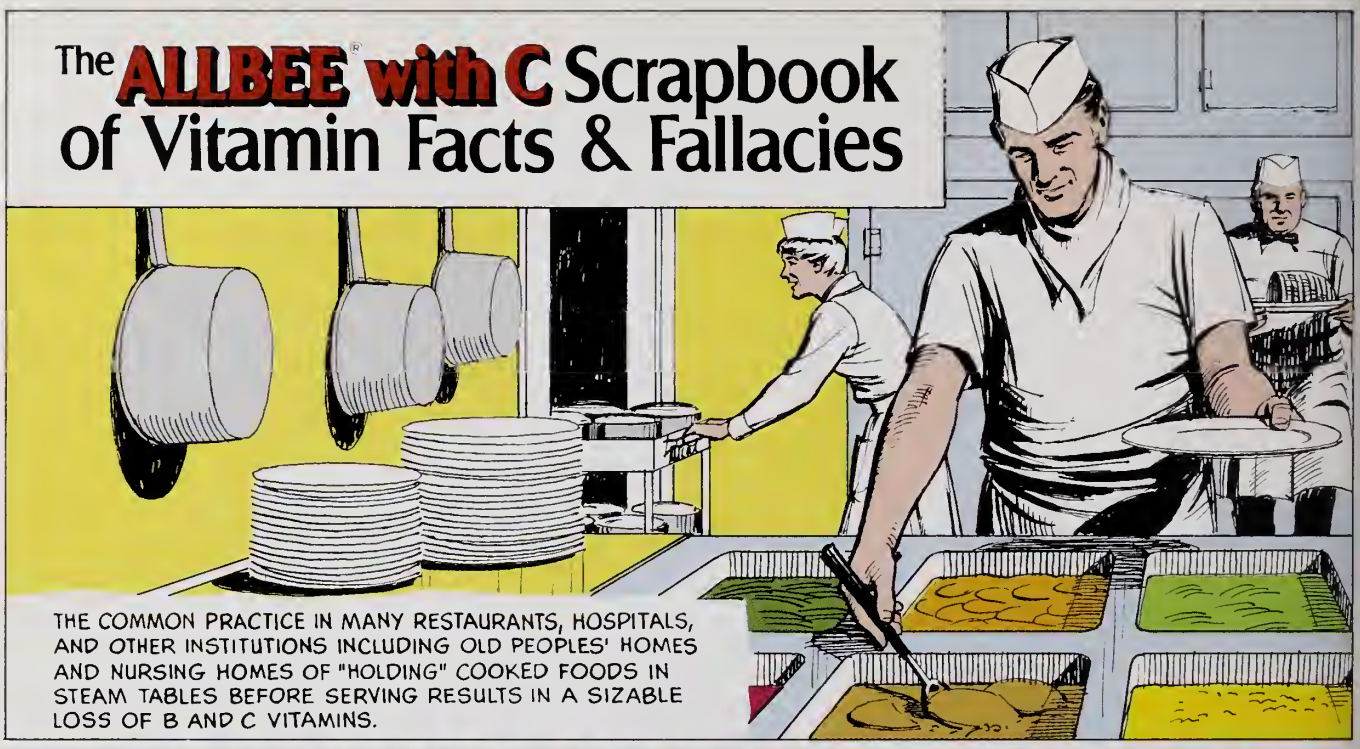
	each tablet, capsule or 5 cc. teaspoonful of elixir (23% alcohol)	each Donnatal No. 2	each Extentab
yoscyamine sulfate	0.1037 mg	0.1037 mg.	0.3111 mg
tropine sulfate	0.0194 mg	0.0194 mg.	0.0582 mg
yoscine hydrobromide	0.0065 mg	0.0065 mg	0.0195 mg
henobarbital	(¼ gr.) 16.2 mg	(½ gr.) 32.4 mg.	(¾ gr.) 48.6 mg

warning: may be habit forming)

Brief summary. Adverse Reactions: Blurring of vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur on higher dosage levels, rarely on usual dosage. Contraindications: Glaucoma; renal or hepatic disease; obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); or hypersensitivity to any of the ingredients.

A·H·ROBINS A. H. Robins Company Richmond Virginia 23220

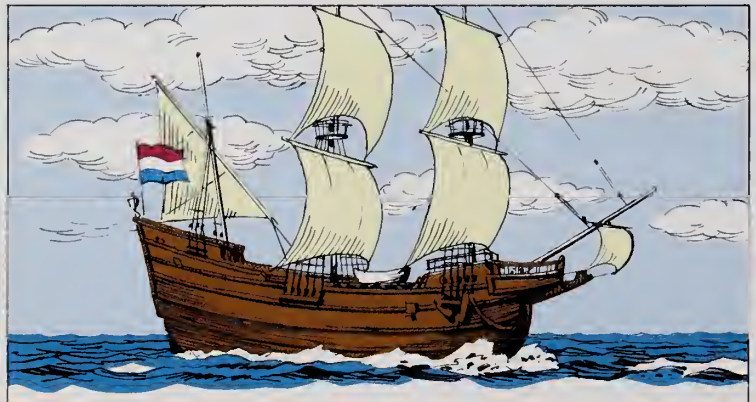
The ALLBEE® with C Scrapbook of Vitamin Facts & Fallacies



THE COMMON PRACTICE IN MANY RESTAURANTS, HOSPITALS, AND OTHER INSTITUTIONS INCLUDING OLD PEOPLES' HOMES AND NURSING HOMES OF "HOLDING" COOKED FOODS IN STEAM TABLES BEFORE SERVING RESULTS IN A SIZABLE LOSS OF B AND C VITAMINS.

DURING THE CIVIL WAR 30,714 CASES OF SCURVY WERE REPORTED, AND 383 DEATHS WERE ATTRIBUTED DIRECTLY TO THE DISEASE.

THE AMOUNT OF SUNLIGHT AVAILABLE DURING RIPENING DETERMINES TO A LARGE EXTENT THE FINAL ASCORBIC ACID CONTENT OF TOMATOES. HENCE, A COOL, WET SUMMER PRODUCES WATERY, LESS TASTY FRUIT THAT'S LOWER IN VITAMIN C.



RONSSENS, A DUTCH PHYSICIAN, WROTE IN 1564 THAT "DUTCH SAILORS WHO, RETURNING FROM SPAIN, WERE ATTRACTED BY THE NOVEL RICHNESS OF THE FRUIT (ORANGES) AND BY THEIR GREED AND GLUTTONY, UNEXPECTEDLY DROVE OUT THE DISEASE (SCURVY), AND HAD THIS HAPPY EXPERIENCE NOT ON A SINGLE OCCASION ONLY, BUT REPEATEDLY."

Available on your prescription or recommendation

ALLBEE® with C

High Potency B-Complex and Vitamin C Formula

A.H. Robins Company, Richmond, Va. 23220 A·H·ROBINS

Bank of America gives fast relief from financial upset three ways:

1. Professional Term Loans. Suffering from lack of funds to update our equipment, remodel or expand our quarters—or just want some extra working capital on-hand? Our financing is designed to meet your special needs, promptly and painlessly, and with flexible terms. (For those just starting practice, financing based on projected income is also available.) And your Bank of America Loan Officer can assist you with leasehold improvements, too.

2. Professional Billing and BankAmericard® Services. Give your business a shot in the arm with one of the most sophisticated financial control systems available. Our customized services streamline bookkeeping, can boost efficiency and profits, and help all aspects of your practice run more smoothly. At a cost that's easy to swallow.

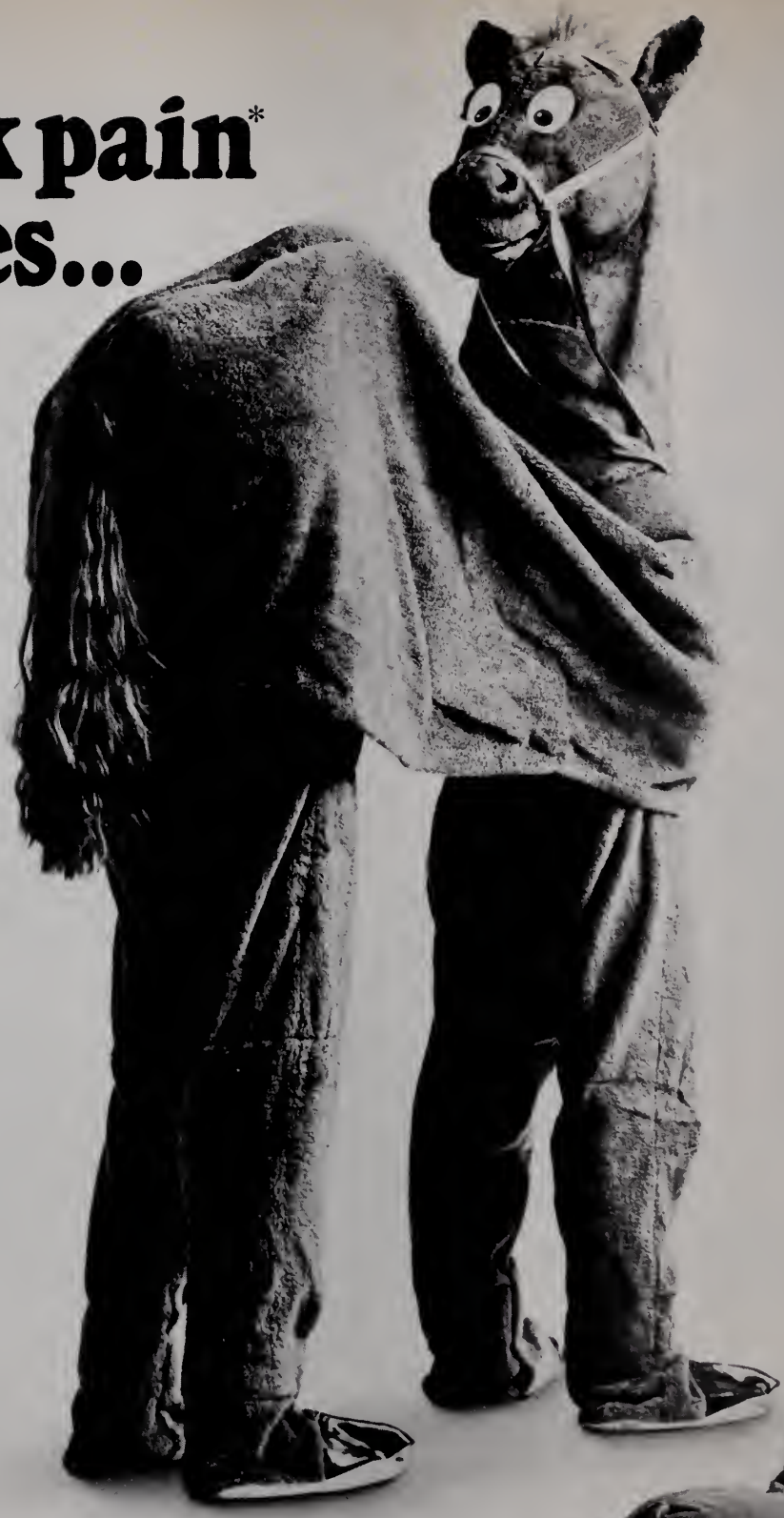
3. Personal Trust Services. Expert management of stocks and bonds, real estate, property and tax matters is your prescription for financial security and peace of mind. Our Trust Officer will work out a plan tailor-made to the individual needs of your family.

With over two decades of administering to the financing needs of medical professionals, you could call us the "Money Specialists." (No other bank can offer you this much experience.) Shouldn't you make an appointment for your financial check-up with Bank of America today? You'll feel a lot better tomorrow.

BANK OF AMERICA

® OF AMERICA NT&SA • MEMBER FDIC

When low back pain* interferes...



Help relieve pain, restore mobility with

PARAFON FORTE® Tablets

PARAFLEX® (chlorzoxazone)† 250 mg.; TYLENOL® (acetaminophen) 300 mg

*This drug has been evaluated as "possibly" effective for this indication.

See brief summary of prescribing information on facing page for Indications, Contraindications, Warnings, Precautions and Adverse Reactions.

© McN 73

PARAFON FORTE® Tablets help relieve pain, restore mobility and stop pain-spasm feedback by providing:

a nonsalicylate analgesic equal to aspirin for relief of pain,[1,2] yet unlikely to cause the gastric irritation,[2,3] allergic reactions[2] or increased bleeding time[4] associated with aspirin therapy.

and a skeletal muscle relaxant shown in extensive clinical studies to be useful in a variety of low back disorders[5-7]* but which is not an antihistamine or tranquilizer derivative and is unlikely to produce a tranquilizing or sedative effect.[8]

***Indications** Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective for the relief of severe skeletal muscle pain and spasm when associated with acute disorders of the lower back (including acute exacerbations of chronic conditions).

Contraindications: Sensitivity to either component.
Warnings: *Usage in Pregnancy*—Use in woman of child-bearing potential only when potential benefits outweigh possible risks.
Precautions: Exercise caution in patients with known allergies or history of drug allergies. If a sensitivity reaction or any signs or symptoms suggestive of liver dysfunction are observed, the drug should be stopped
Adverse Reactions: Occasionally, drowsiness, dizziness, lightheadedness, malaise, overstimulation or gastrointestinal disturbances may be noted; rarely, allergic-type skin rashes, petechiae, ecchymoses, angioneurotic edema or anaphylactic reactions. In rare instances, *Paraflex* (chlorzoxazone) may possibly have been associated with gastrointestinal bleeding While *Paraflex* (chlorzoxazone) and chlorzoxazone-containing products have been suspected as being the cause of hepatic toxicity in approximately eighteen patients, it was not possible to state that the dysfunction was or was not drug induced
Usual Adult Dosage: Two tablets q.i.d.
Supplied: Scored, light green tablets, imprinted "McNEIL"—bottles of 100.

References: 1. Batterman, R.C., and Grossman, A.J Fed Proc. *14* 316, 1955 2. Goodman, L.S., and Gilman, A., ed. The Pharmacological Basis of Therapeutics, ed 4 New York. The Macmillan Company, 1970. 3. Vickers, N Gastroint Endosc *14* 94, 1967 4. Mielke, C.H., Jr, and Britten A.F.H. New Engl J. Med *282* 1270, 1970 (Corresp.) 5. Vernon, W.G Curr Therap Res *14* 801, 1972 6. Scheiner, J.J Curr Therap Res. *14* 168, 1972. 7. Walker, J.M Curr Therap Res. *15* 248, 1973 8. Friend, D.G Clin Pharmacol Ther *5* 871, 1964

†U.S. Patent No 2,895,877

McNEIL McNeil Laboratories, Inc.
Fort Washington, Pa 19034

Beautiful new idea at Lake Tahoe: Rent now—Pay later!

For your summer vacation, rent a 2, 3 or 4-bedroom home on Lake Tahoe's magnificent north shore—then take 12 months to pay. Payments as low as $8 per month. No interest or carrying charge. Luxurious new units are completely furnished. Fireplaces, pool, cabana, tennis. Group packages available. Send coupon for more information.

YES! Tell us more about the Lake Forest Glen vacation rental program.

Name _____

Address _____

City _____ State _____

Zip _____ Phone _____

Send to: Lake Forest Glen,
Post Office Drawer N, Sausalito, CA 94965 WJM

Case history #5

Wayne's well-being comes first.

Wayne's being well comes first.

For two weeks in 1972, Wayne Patton lay unconscious in an Oxnard hospital. Wayne, a deputy sheriff for Ventura County, sustained serious injuries when his patrol car crashed on the way to a robbery scene. The accident left him partially paralyzed and caused disruptions in his ability to see, speak, and walk.

As soon as Wayne was sufficiently recovered, State Fund arranged for his transfer to the Santa Barbara County Rehabilitation Center, where he was given extensive rehabilitation therapy. He made rapid progress toward recovery.

After three months of care, Wayne left the hospital. He was ready to rebuild his life, and State Fund was ready to help. After arranging for continued physical therapy and outpatient medical care, the State Fund staff enrolled him in Work, Inc., a sheltered workshop in Santa Barbara, and also arranged for his friends at the Sheriff's Department to drive him to and from the workshop. In his first week at the shop, Wayne threw away his cane.

Although he was unable to take his old job back, State Fund worked hard to find him a position in a related field. Today, Wayne Patton works full-time as an Air Pollution Control Monitor.

It took a lot of hard work and courage for Wayne to rebuild his life. Most of the credit belongs to him, but a lot of people helped: his wife, his doctors, his friends at the Sheriff's Department, and the people at State Fund.

Conserving your human resources is our only business

STATE COMPENSATION INSURANCE FUND

(Continued from Page 26)

SITUATIONS WANTED

PATHOLOGIST, 39, AP-CP certified, seeks position as Associate or Director, available July. Box 9380, Western Journal of Medicine, 731 Market Street, San Francisco 94103.

OB-GYN, board certified, 53, good health, wishes part-time work; administration, family planning; Gyn clinic or surgery including abortions. Sonoma County, adjacent areas. Box No. 9381, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

LOCUM TENNENS WANTED

LOCUM TENENS needed for June and July—Internal Medicine, with opportunity for association to follow. Box 9384, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

LOCUM TENENS RADIOLOGIST desired for July and August 1974 to work in 180-bed community hospital in Southern California. Reply to Robert E. Rafferty, MD, 26087 Stardust St., Hemet, CA 92343. Phone (714) 658-9471, Ext 324.

REAL ESTATE FOR SALE

FOR SALE—2.32 Acres in choice Walnut Creek location zoned for medical offices. Close to other medical-dental offices and regional shopping center. Listed price is $275,000. Plat map and aerial photo are available. Call LARRY K. SMITH, JR., Realtor, Financial Center Building, 1615 Bonanza St., Suite 320, Walnut Creek, CA 94596; (415) 933-2550 anytime.

MOUNTAIN CABIN FOR SALE

DOCTORS IDYLLWILD MT. CABIN. 2 bedrooms, 1½ baths. VIEW, pines and sun. Gas heat and fireplace. $27,500 furnished. Phone (714) 328-4827.

ISLAND PROPERTY FOR SALE

SECLUSION ON READILY ACCESSIBLE ISLAND—A few large waterfront sites on non-ferry-served San Juans Island. FOR THE ENVIRONMENTALLY CONCERNED—eagles and osprey, otters and abalone, virgin timber and grassy sunlit clearings, all with mountain views. One of the last opportunities to own and enjoy permanent protection from the onslaught of humanity in a natural setting. Your pleasure and investment in this rapidly disappearing non-renewable resource are protected by covenant. Priced well below comparables, starting at $32,500. Offered by owner. Residence phone: (206) 454-1771. Business phone: (206) 455-1960.

HAWAIIAN VACATION HOME FOR LEASE

FLY, DON'T DRIVE—HAWAIIAN (Hanalei, Kauai) VACATION beach home for only $750 per month. Old Hawaiian atmosphere, away from crowded beaches. Excellent skin diving, swimming, and beaches. Sleeps 12. Available April 8 to April 27, May 11 to May 31, and after September 8. Weekly rate $200. For details, pictures, and information, write James R. Christiansen, 1216 State Street, Santa Barbara, CA 93101, telephone (805) 962-8141.

5th INTERNATIONAL CONGRESS OF SOCIAL PSYCHIATRY

ATHENS SEPT. 1-7, 1974

14-day independent tour from August 29-September 12 Inclusive. Jet roundtrip LAX-Athens, accommodations in doubles with bath, superior class hotel, breakfasts, dinners, 4-day cruise with 3 meals daily, transfers, guides, social program for dependents.

FOR RESERVATIONS, INFORMATION AND BROCHURE CONTACT:

American Student Travel Association
Department CIANS
924 Westwood Boulevard, at UCLA
Los Angeles, CA 90024
Telephone (213) 479-4444

HOUSE TO RENT

SPACIOUS LAKE TAHOE HOUSE for rent July, August, three bedrooms, three baths, plus loft. G. Tolbert, P.O. Box 963, Tahoe City, CA 95730; (916) 583-4445.

OFFICES FOR LEASE OR RENT

OFFICE FOR RENT: 2,109 sq. ft. Ideal location, center of town, across the street from large hospital. Ophthalmology suite or will partition to suit any medical practice. Write or phone Dr. Mario R. Galliano, 204 West College Street, Covina, California 91723, (213) 332-7112.

ANGELICI MEDICAL BUILDING—Space for General Practitioner or Specialist—New four suite professional building will be completed August, 1974. 150 feet from entrance of Huntington Beach Inter Community Hospital. Suite may be purchased or leased. Contact Arnold Angelici, DDS, 17612 Beach Blvd., Huntington Beach, CA 92647; (714) 842-2549.

BERKELEY, CALIFORNIA—Good opportunity for Internist to establish private practice, or Family Practitioner, at Dwightmil Medical Center, 2505 Milvia St., adjacent to Herrick Hospital. Phone (415) 845-2391.

FOR RENT MEDICAL SUITE, ideal location 26th and Geary Boulevard. $275 month. Four examination rooms, private office, x-ray room, reception and waiting rooms. For appointment: N. Kanatoff, evenings (415) 665-7523.

OFFICE SPACE AVAILABLE SAN FRANCISCO—3 treatment rooms, laboratory and consultation rooms, private and business offices, large reception room, private and public parking. Eureka Valley neighborhood, dense population area, excellent public transportation. Rent: $350; Call (415) 863-8100.

FOSTER PARENTS WANTED

FOSTER PARENTS for private agency needed on a long-term basis for children 5-15 years. Need parents with understanding and ability to cope. Can compensate commensurate with child's problems and needs. Will consider single parents with special experience. Casey Family Program, (415) 574-4292.

TEXTBOOKS FOR SALE

MANUAL OF ROUTINE ORDERS FOR MEDICAL AND SURGICAL EMERGENCIES
published by
WARREN GREEN, Inc.
10 South Brentwood Boulevard
St. Louis, Missouri 63105

PHYSICIAN SPECIALIST, MD

Department of Medicine of a university teaching hospital in So. Calif. offers full-time position to Generalist or Internist, to provide primary medical coverage on a Post-trauma Orthopedic Service. Some background and interest in Orthopedics desirable. If interested, send C.V. to **R. E. BODFISH, MD,** Rancho Los Amigos Hospital, 7601 E. Imperial Highway, Downey, CA 90242. Equal opportunity for qualified women and minority groups.

SACRAMENTO, CALIFORNIA

FOUNDATION-SPONSORED PRIMARY CARE GROUP

Excellent opportunity for four Board-eligible FAMILY PRACTITIONERS in new modern facilities in the heart of rapidly growing community. Great hospital access. Positions available beginning May 1, 1974. Annual minimum salary of $20,000 guaranteed from fee-for-service practice. Position includes eligibility for appointment to University of California-Davis School of Medicine teaching staff. Positions too attractive to delay. Send confidential curriculum vitae to:

CHARLES B. FRENCH, MD
Project Director

MEDICAL CARE FOUNDATION OF SACRAMENTO
650 Howe Avenue
Sacramento, California, 95825

LOOKING FOR INCOME?

PETRO-LEWIS OIL INCOME PROGRAM . . .
A Limited Partnership
Emphasizing Income
from Producing
Oil and Gas Properties

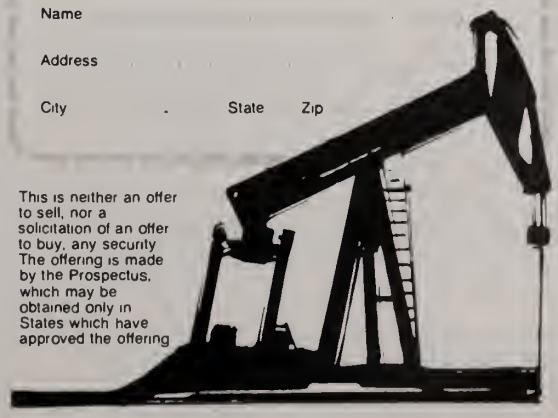
NO DRILLING

For a free prospectus, write:
Medi-Fund Financial Corp.
525 Spruce Street
San Francisco, CA 94118

Name

Address

City State Zip



This is neither an offer to sell, nor a solicitation of an offer to buy, any security. The offering is made by the Prospectus, which may be obtained only in States which have approved the offering

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine,** Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

ALCOHOLISM AND DRUG USE

June 24-28—**Institute on Drug Dependency.** LLU. Monday-Friday. $75. Contact: Center for Dependent Behavior, LLU School of Health, Loma Linda 92354.

CANCER

July 22-25—**Cancer of the Skin and Mouth—Advances in Diagnosis and Treatment.** STAN. Monday-Thursday. 28 hrs. $200.

September 7-8—**Early Diagnosis of Breast Cancer.** UCLA. Saturday-Sunday.

Continuously—**Tumor Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. Tuesdays, 4:00 p.m. Contact: Sidney Saltzstein, MD, University Hospital, San Diego. (714) 291-3330, ext. 1071.

Continuously — **Tumor Board — Harbor General Hospital.** Pathology Conference Room, Harbor General Hospital, Torrance. Fridays 3-4 p.m. Advice and consultation from specialists (UCLA faculty members) in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: John R. Benfield, MD, Dept. of Surgery, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 281.

MEDICINE

May 15—**Sickle Cell Seminar on Current Research.** Charles R. Drew Postgraduate Medical School and King-Drew Sickle Cell Center at Claude Hudson Auditorium, Los Angeles. Wednesday. Contact: Duane Dillman, EdD, Coordinator of Cont. Ed., 1620 E. 119th St., Los Angeles 90059.

May 15—**The Patient with Edema: New Concepts, Approaches, Problems.** UCLA. Wednesday.

May 17—**California Heart Association—Scientific Sessions for Physicians.** Erawan Garden Hotel, Indian Wells. Friday. $25. Contact: Marilyn Probst, CHA, 1370 Mission St., San Francisco. (415) 626-0123.

May 19-20—**Peptic Ulcer Disease.** American Gastroenterological Association at Hilton Hotel, San Francisco. Sunday-Monday. $100 for members; $125 non-members. Contact: AGA Postgraduate Course-Peptic Ulcer, 6900 Grove Rd., Thorofare, N.J. 08086.

May 19-25—**American Gastroenterological Association.** Hilton Hotel, San Francisco. Sunday-Saturday. Contact: Mr. Charles B. Slack, Exec. Sec., AGA, 6900 Grove Rd., Thorofare, N.J. 08086.

May 20-21—**Gastrointestinal Endoscopy—4th Postgraduate Course.** American Society for Gastrointestinal Endoscopy at Hilton Hotel, San Francisco. Monday-Tuesday. $75 for ASGE members; $100 for non-members. Contact: J. Alfred Rider, MD, Dir., ASGE Postgraduate Course, 350 Parnassus, Suite 900, San Francisco 94117.

May 20-22—**Heart and Lung Disease in Neonates and Infants.** UCLA at Ahwahnee Hotel, Yosemite National Park. Sunday-Wednesday. For Southern Calif. physicians only.

May 22—**Coronary Rehabilitation.** USC. Wednesday.

May 22—**American Society for Gastrointestinal Endoscopy.** Hilton Hotel, San Francisco. Wednesday. Contact: Bernard M. Schuman, MD, Sec., ASGE, 2799 W. Grand Blvd., Detroit 48202.

May 23-25—**Cardiologists' Appraisal of Operative Heart Disease.** PMC at St. Francis Hotel, San Francisco. Thursday-Saturday.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

June 18-July 30—**Advances in Hematology.** UCD Extension at St. Joseph's Hospital, Stockton. Tuesdays, 7:30-9:30 p.m. $40. Contact: Rene Mack, University Extension, UCD, Davis 95616.

June 21-23—**Coronary Disease/Exercise Testing/Rehabilitation Therapy.** International Medical Corp. at Fairmont Hotel, San Francisco. Friday-Sunday. $175. Contact: William E. James, Ph.D., Dir. of Professional Education, International Medical Corp., 2865 S. Colorado Blvd., Denver, Colo. 80222. (303) 757-7875.

July 27—**New Concepts in Respiratory Therapy Management.** UCD. Saturday.

September 13—**Course in Armchair Allergy.** PMC. Friday.

September 19-21—**The Relevance of Animal Models to Human Dermato-Pharmacology and Dermato-Toxicology.** UCSF. Thursday-Saturday. 11 hrs. $200.

Continuously—**Recertification Review Course—Internal Medicine.** USC at Louis B. Mayer Medical Teaching Center, Keith Admin. Bldg. Tuesdays and Thursdays, 7-10 p.m. April 9-October 10, 1974. Sessions will cover 9 broad topics of internal medicine; each topic will have 5 evening sessions.

Continuously—**Clinical Conferences.** Community Hospital of Santa Cruz. See Of Interest to All, Continuously.

Continuously—**Medical Chest Conference.** St. Mary's Hospital, San Francisco. Tuesdays, 4:00-5:00 p.m. in Pulmonary Classroom. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Medical Morbidity-Mortality Conference.** St. Mary's Hospital, San Francisco. Thursdays, 12:15-1:00 p.m. in Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Clinical Cardiology Conferences.** San Diego County Heart Association at University Hospital, San Diego. Thursdays, 8-10 p.m. Contact: Robert O'Rourke, MD, Instructor, Univ. Hospital, San Diego. (714) 291-3330, ext. 1644. Or Mrs. Cathy Ware, Prog. Dir., San Diego Co. Heart Assn., 3640 5th St., San Diego 92103. (714) 291-7454.

Continuously — **Differential Diagnosis in Internal Medicine.** USC. Fourth Thursday of each month, 7:30-10:00 p.m. September 27, 1973-May 30, 1974.

Continuously—**Renal Dialysis Traineeships.** UCSF. By special arrangement.

Continuously—**Preceptorships in Biochemistry and Biophysics.** UCSF. By arrangement.

Continuously—**Clinics in Dermatology.** UCSF. By arrangement.

Continuously—**Cardiovascular Seminars.** Mondays at 4:30 p.m. in the second floor lecture hall, Basic Science Building, UCSD. Contact: UCSD.

Continuously—**Preceptorships in Cardiology.** American College of Cardiology and PMC. By arrangement. Contact: Arthur Selzer,, MD, PMC; or Miss Mary Anne McInerny, ACC, 9650 Rockville Pike, Bethesda, Md. 20014. (301) 530-1600.

Continuously—**Biomedical Lecture Series.** UCSD. Specified Wednesday at 8:00 p.m. For schedule contact UCSD.

Continuously—**Joint Continuing Medical Education Programs for South Bay Hospitals.** UCSD, Bay General Hospital, Chula Vista Community Hospital, Coronado Hospital, Paradise Valley Hospital and CRMP. Programs to be held at various hospitals. Contact: UCSD.

Continuously—**Renal Conference.** San Joaquin General Hospital, Stockton. First Thursday of each month, 11:00 a.m. to 12:00 noon, Conference Room 2. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Wednesday of each month, 10:00-11:30 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Seminar in Clinical and Public Health Aspects of Chest Diseases.** Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Three-hour sessions on second Friday of every other month, 9-12 a.m., B-3 classroom, Chest Wards. Presentation of patients demonstrating medical, social, and public health aspects of chest disease, followed by discussion of cases. Course open to physicians, nurses, social workers and personnel concerned with detection and management of patients with chest disease. No fee. Contact: Matthew Locks, MD, Dir., Chest Ward Service, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1245.

Continuously—**Training of Physicians in Modern Concepts of Pulmonary Care.** CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George C. Burton, MD, LLU.

Continuously—**Continuing Education in Internal Medicine—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12:00-1:00 p.m. Systematic review of internal medicine, lectures by faculty and visiting professors. Contact: A. James Lewis, MD, Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1534.

Continuously—**Training for Physicians in General Internal Medicine.** CRMP Area VI and LLU at LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

Continuously—**Cardiology Conferences — CRMP Area III.** Monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations of local complicated cardiological problems. Contact: William J. Fowkes, Jr., MD, 703 Welch Road, Suite G1, Palo Alto 94304. (415) 321-1200, ext. 6015.

Grand Rounds—Medicine

Tuesdays

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

9:00-10:00 a.m., Morrissey Hall, St. Mary's Hospital, San Francisco.

Neurologist in Chief Rounds. 12:30 p.m., 6 East, University Hospital of San Diego County, San Diego. UCSD.

Wednesdays

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

1st Wednesday of each month, 10:00-11:15 a.m., Conference Room 1, San Joaquin General Hospital, Stockton.

10:30-12 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:00 noon. Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., University Hospital, UCSD.

12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

Thursdays

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

10:30-12:00 noon, Room 63-105, UCLA Medical Center. UCLA. Second, Third, and Fourth Thursdays.

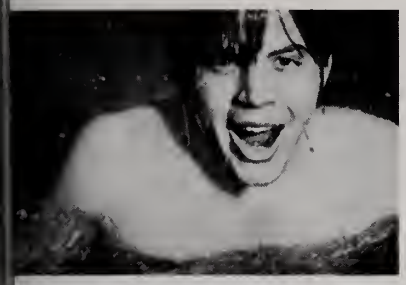
Neurology. 11:00 a.m., 664 Science, UCSF.

(Continued on Page 37)

second wind for bronchospastics
QUIBRON PLUS®
Each capsule or tablespoon (15 ml.) elixir contains: theophylline (anhydrous) 150 mg., glyceryl guaiacolate 100 mg., ephedrine HCl 25 mg., and butabarbital 20 mg. (Warning: may be habit-forming). Elixir: alcohol 15%
the balanced bronchodilator
• Quibron Plus provides a balance of bronchodilation, sedation, and expectorant activity in a unique formulation
• theophylline PLUS ephedrine for relief of bronchiolar constriction
• PLUS glyceryl guaiacolate to facilitate expectoration
• PLUS butabarbital, the mild, intermediate-acting sedative
Mead Johnson LABORATORIES
For brief summary, please see facing page.

QUIBRON PLUS®

ach capsule or tablespoon (15 ml.) elixir contains: heophylline (anhydrous) 150 mg., glyceryl guaiaolate 100 mg., ephedrine HCl 25 mg., and butabarital 20 mg. *(Warning: may be habit-forming).* Elixir: cohol 15%



r comprehensive relief many bronchospastic disorders

Indications: Based on a review of a similar drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: bronchial asthma; bronchitis, bronchiectasis, and emphysema in which bronchospasm is present; the relief of bronchospasm; hay fever; nasal allergy; or for use as an expectorant.
Final classification of the less-than-effective indications requires further investigation.

osage: Adults: 1-2 capsules or 1-2 blespoons elixir 2-3 times daily. Children 8 to 12: 1 capsule or 1 tablespoon xir (15 ml.) 2-3 times daily. Children der 8: Up to ½ teaspoon (2.5 ml.) xir per 10 lb. body weight, 2-3 times ily. Dosage should be adjusted on individual basis.
ntraindications: Contraindicated in tients who are sensitive to any ingedient of the formulation.
ecautions: Do not administer more quently than every 6 hours, or within hours after rectal dose of any preparation containing theophylline or inophylline. Do not give other compunds containing xanthine derivates concurrently. Use cautiously in tients with cardiovascular disease, ertension, hyperthyroidism, prostic hypertrophy, hepatic disease, impred renal function, glaucoma, diabes. Do not exceed recommended se. Be aware of the possible effects m concomitant doses of other sympthomimetic amines. Caution parents inst overdosage in children.
verse Reactions: Theophylline may rt some stimulating effect on the tral nervous system. Its administion may cause local irritation of the tric mucosa, with possible gastric comfort, nausea, and vomiting. Takin Quibron Plus after meals may help id such disturbances. *Central Nervous System:* Nervousness, jitteriness, tigo, and sedation; *Cardiovascular:* ycardia (palpitation); *Miscellaneous:* Precordial pain.
Supplied: Elixir in bottles of 1 pint; sules in bottles of 100.

Mead Johnson
LABORATORIES

©1973 MEAD JOHNSON & COMPANY
EVANSVILLE, INDIANA 47721 U.S.A. 734022

(Continued from Page 35)

Neurology. 12:30 p.m., University Hospital of San Diego County, San Diego. UCSD.

4th Thursday of each month, 12:30 p.m. in lower conference room, Huntington Intercommunity Hospital, Huntington Beach.

Fridays

8:00 a.m., Auditorium, First Floor, Kern County General Hospital, Bakersfield. UCLA.

8:30 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. UCLA. Second and Fourth Fridays.

Neurology. 8:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

1st and 3rd Fridays, 8:30 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. UCLA.

Clinicopathologic Conference. 1st Friday, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

Internal Medicine. 2nd, 3rd, and 4th Fridays, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

MENTAL RETARDATION

May 19-31—**Mental Retardation.** UCLA. 13 days.

May 23-24—**Aspects of Mental Retardation.** USC. Thursday-Friday.

September 29-October 11—**Mental Retardation.** UCLA. 13 days.

OBSTETRICS AND GYNECOLOGY

May 17—**Regionalization of Obstetrics and Nursery Services.** CMA and Hospital Council of Northern California at Stanford Court Hotel, San Francisco. Friday. $20. Contact: Richard Manley, CMA.

May 17-18—**Fetal Monitoring.** Memorial Hospital Medical Center-UCI Center for Health Education at Memorial Hospital Med. Ctr., Long Beach. Friday-Saturday. $50. Contact: D. V. Prian, MD, Memorial Hospital Med Ctr., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

Continuously—**Ob/Gyn Conference.** San Joaquin General Hospital, Stockton. Mondays, 12:00-1:30 p.m. in Doctors' Dining Room. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. See Radiology and Pathology, Continuously.

Grand Rounds—Obstetrics and Gynecology

Mondays

10-11:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Tuesdays

9:00 a.m., Fifth Floor Auditorium, Room 53-105, UCLA Medical Center. UCLA.

Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Center, Sacramento. UCD.

Fridays

8:00 a.m., Auditorium, Orange County Medical Center. UCI.

(Continued on Page 43)

At Your Service in The Golden State

In the region named *California* by Spanish adventurers probably after the name of a treasure island in a popular Spanish tale . . .

PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY, MISSOURI 64137

is represented by . . .

Dick Bastin

Vito Bell

Mel Bergman

Barry Bialkoski

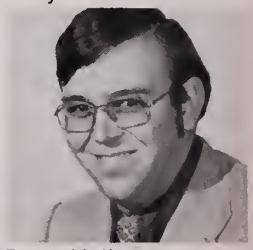
Larry Carver

Dave Evans

Bob Fatch

Richard Foss

Dave Hawks

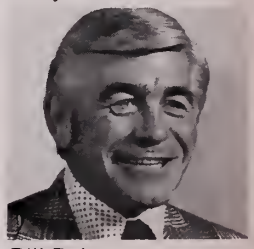

Barry Heilman

Bob Jones

Randy Kennick

Ruth MacKie

Marty Myers


Bill Palmer

John Patella

Jim Petric

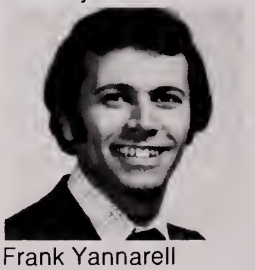
Mike Ryan

Bud Sinkey

Ernie Smith

Bill Stauch

Lorin Waxman


Frank Yannarell

These representatives bring you . . . . . .

Puts comfort in your prescription for nicotinic acid

[illegible] Each capsule contains 400 mg of [illegible] base that provides [illegible] effect [illegible] NICO-400® is recommended for all [illegible] has [illegible] and for [illegible] acid [illegible] individuals with a [illegible] acid severe [illegible] or [illegible] Use with caution in these patients [illegible] severe diabetes [illegible] and [illegible] be [illegible] therapy [illegible] and Administration. One [illegible] is directed by [illegible] Federal law prohibits [illegible] Bottles of 100 [illegible]

[illegible] patient benefit product from

PHARMACEUTICAL DIVISION
MARION
LABORATORIES, INC.

THE OPTIMAL DOSE, 400-mg, timed-release NICO-400® (nicotinic acid) capsule provides

- Controlled flushing for the desired effects without therapy-limiting side effects.
- Convenient b.i.d. dosage that's less likely to be forgotten.
- The economy of nicotinic acid medication.

For comfort wherever nicotinic acid is used

NICO-400®

(nicotinic acid) Plateau CAPS®

Part of a series on the clinical, bacteriological and pharmacological aspects of Bactrim therapy.

This is Bactrim™ against E. coli, Proteus

These are results from clinical trials* in which patients with chronic urinary tract infections (primarily cystitis, pyelitis and pyelonephritis), more than half with obstructive complications, were treated with Bactrim for 10 days and evaluated at intervals up to 32 days after termination of therapy. Patients were considered to have a significant bacteriological response when the urine culture revealed 10,000 or fewer colonies/ml of any single organism cultured from a midstream clean-catch specimen.

Before prescribing Bactrim, please consult complete product information for all adverse reactions, contraindications, precautions and warnings.

ROCHE

performance
spp. and Klebsiella

	Excellent initial response* after 10 days of therapy	Impressive response maintained 32 days after termination of therapy
n E. coli infections	97.1% of 105 patients	73.1% of 93 patients
n Proteus spp. infections	81.1% of 37 patients	60.0% of 35 patients
n Klebsiella infections	85.7% of 21 patients	65.0% of 20 patients

Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley, New Jersey

Bactrim™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

In cystitis, pyelonephritis and pyelitis diagnosed as chronic and due to susceptible urinary tract pathogens, usually E. coli, Klebsiella-Enterobacter and Proteus mirabilis.

Please see following page for summary of product information.

In cases of cystitis, pyelonephritis and pyelitis diagnosed as chronic*

Bactrim™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

- aggressive antibacterial activity
- interrupts essential metabolic process of susceptible organisms, usually E. coli, Klebsiella-Enterobacter, P. mirabilis, and, less frequently, indole-positive proteus species
- over 91% initial efficacy in clinical studies of patients with urinary tract infection diagnosed as chronic*
- impressive response even in cases with obstructive complications
- not recommended for children under 12, during pregnancy or the nursing period
- no loading dose; two tablets b.i.d. recommended for 10-14 days

*due to susceptible organisms

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Enterobacter, Proteus mirabilis,* and, less frequently, indole-positive proteus species).

NOTE: The increasing frequency of resistant organisms limits the usefulness of antibacterials, especially in chronic and recurrent urinary tract infections.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia in elderly patients on diuretics, primarily thiazides. Sore throat, fever, pallor or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted. Data are insufficient to recommend use in infants and children under 12.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, allergy or bronchial asthma; and in those with glucose-6-phosphate dehydrogenase deficiency, where hemolysis may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritu exfoliative dermatitis, anaphylactoid reactions, periorbital edem conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, sto matitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, ment depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *M cellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Du to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfon mides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agent may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for children under 12. Usual adult dosage: Two tablets b.i.d. for 10 to 14 days. For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regim
15-30	2 tablets every 24 hou
Below 15	Use not recommende

Supplied: Tablets, each containing 80 mg trimethoprim and 400 sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packag of 100; Prescription Paks of 40, available singly and in trays of 1

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

(Continued from Page 37)

10:30 a.m., Auditorium, Women's Hospital, Los Angeles County-USC Medical Center, Los Angeles. USC.

Saturdays

8:00 a.m., Executive Dining Room, University Hospital of San Diego County, San Diego. UCSD.

PEDIATRICS

May 17—**Regionalization of Obstetrics and Nursery Services.** See Obstetrics and Gynecology, May 17.

May 20-22—**Heart and Lung Disease in Neonates and Infants.** See Medicine, May 20-22.

June 13-14—**Infant Sensory Dysfunction.** USC. Thursday-Friday.

June 16-20—**1974 Birth Defects Conference.** Attending Staff Association, Harbor General Hospital at Newporter Inn, Newport Beach. Sunday-Thursday. Contact: David Rimoin, MD, Harbor Gen. Hosp., 1000 W. Carson, Torrance 90509. (213) 328-2380, ext. 1441.

June 21—**13th Annual Conference on Prematurity.** STAN. Friday.

September 11-12—**Brennemann Memorial Lectures—31st Annual.** Los Angeles Pediatric Society at Sportsmen's Lodge, North Hollywood. Wednesday-Thursday. Contact: Mrs. Eva Black, Exec. Sec., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

Continuously—**Perinatal Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 12:30 p.m., Conference Room. Contact: Marguerite Markarian, MD, Dir. of Nurseries, Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3261.

Continuously—**Pediatric Clinical Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 8:00 a.m., Conference Room "H." Contact: Harry W. Orme, MD, Med. Dir., Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3228.

Continuously—**Preceptorships in Pediatrics.** UCSF. By arrangement.

Continuously—**Pediatric Cardiology Conference.** UCSD, Third Floor Conference Room, University Hospital. Clinical review of cases planned for the week, Tuesdays at 7:30 a.m.; Clinical review of data obtained, Fridays at 1:30 p.m. Contact: UCSD.

Continuously—**Pediatric Research Seminar.** UCSD. Mondays, 12 noon-1:00 p.m.

Continuously—**Pediatrics Clinical Conference.** San Joaquin General Hospital, Stockton. Wednesdays, 10:00-11:15 a.m., and Fridays, 9:30-11:00 a.m., Conference Room 3. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric-Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Thursday of each month, 9:30-11:00 a.m., Conference Room 2. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric Cardiology Conference.** St. Vincent's Hospital, Los Angeles. Fourth Thursday of each month, 2:00 p.m., Main Doheny Conference Room. Contact: Leonard M. Linde, MD, Chief, Pediatric Cardiology, St. Vincent's Hospital, 3rd and Alvarado Sts., Los Angeles.

Continuously — **Pediatric Conference.** Cedars-Sinai Medical Center, Los Angeles. Thursdays weekly, 8:30-9:30 a.m. Contact: B. M. Kagan, MD, Lebanon Hall, Cedars-Sinai Med. Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 181.

Grand Rounds—Pediatrics

Tuesdays

8:00 a.m., Children's Hospital Medical Center, Oakland.

8:30 a.m., Room 4-A, Kern County General Hospital, Bakersfield. UCLA.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

8:30 a.m., University Hospital of San Diego County, San Diego. UCSD.

11:30 a.m., Auditorium, Pediatric Pavilion, Los Angeles County-USC Medical Center, Los Angeles. USC.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Children's Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Children's Hospital, San Francisco.

Thursdays

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:00 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA.

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Pediatric Cardiology. 1st Friday of each month. 8:00 a.m., 5th floor Ward, St. Vincent's Hospital, Los Angeles.

8-9:00 a.m., Lecture Hall, Children's Hospital of Los Angeles.

8:30 a.m., Room M104, Stanford University Medical Center, STAN.

8:30-9:30 a.m., alternately at St. Mary's, Children's, Mt. Zion, and Kaiser Hospitals, San Francisco.

9:30-11:00 a.m., Conference Room 2, San Joaquin General Hospital, Stockton.

Infectious Disease. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

PSYCHIATRY

May 18—**Teenage Sexual Problems and the Physician.** USC Continuing Education in Psychiatry at Hastings Auditorium, Hoffman Bldg., USC. Saturday. 6 hrs. $35. Contact: Donald H. Naftulin, MD, Dir., Cont. Ed. in Psych. USC Sch. of Med., 2025 Zonal Ave., L.A. 90033. (213) 225-1511, ext. 336.

June 1—**Stress.** UCSF. Saturday.

June 12—**The Impotent Male and the Liberated Female.** UCSF at Community Hospital, Santa Cruz. Wednesday.

June 22-23—**Biofeedback: Theory and Clinical Applications.** UCD Extension at Stockton State Hospital, Stockton. Saturday-Sunday. Contact: Rene Mack, University Extension, UCD, Davis 95616.

June 24-28—**Comparative Psychotherapies.** USC Continuing Education in Psychiatry at Hilton Inn, San Diego. Monday-Friday. 20 hrs. $100. Contact: Donald H. Naftulin, MD, Dir., Cont. Ed. in Psych., USC. (213) 225-1511, ext. 336.

July 3-7—**Biofeedback for Physicians.** UCLA at Lake Arrowhead. Wednesday-Sunday.

Continuously—**Adolescent Case Review.** St. Mary's Hospital, San Francisco. Wednesdays, 1:00-2:00 p.m., 3 West Conference Room. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Preceptorships in Psychiatry.** UCSF. By arrangement.

Grand Rounds—Psychiatry

Wednesdays

10:30 a.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

11:00 a.m., McAuley Institute, St. Mary's Hospital, San Francisco.

RADIOLOGY AND PATHOLOGY

May 18—**Nuclear Medicine 1974—Tumor Localization, Bone and Bone Marrow Scanning.** UCD; Sierra Valley Nuclear Medicine Assn; No. Calif. Chapter, Society of Nuclear Medicine at Senator Hotel, Sacramento. Saturday. 4½ hrs.

May 31-June 2—**Radiology of the Pediatric Chest.** American College of Radiology at San Diego. Friday-Sunday. 15 hrs. $200 for members; $240 for non-members. Contact: ACR, 6900 Wisconsin Ave., Chevy Chase, Md. 20015.

June 11-14—**Society of Nuclear Medicine.** Town and Country Hotel, San Diego. Tuesday-Friday. Contact: Margaret Glos, Exec. Dir., SNM, 305 E. 45th St., N.Y. 10017.

September 22-23—**Society for Pediatric Radiology.** Hilton Hotel, San Francisco. Sunday-Monday. Contact: John P. Dorst, MD, Johns Hopkins Hospital, Baltimore, Md. 21205.

September 24-27—**American Roentgen Ray Society.** Hilton Hotel, San Francisco. Tuesday-Friday. Contact: Ted F. Leigh, MD, Emory University Clinic, Atlanta, Ga. 30322.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. Mondays, 12:00 noon, Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Pathology Conference.** St. Mary's Hospital, San Francisco. 2nd and 4th Wednesdays. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Tumor Board.** St. Mary's Hospital, San Francisco. Mondays, 8:00-9:00 a.m., Clinic Building, Room 3. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Clinical Pathology Conference.** St. Mary's Hospital, San Francisco. Third Tuesday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Radiology Film Reading Sessions.** Orange County Radiology Society and Orange County Medical Center at Orange County Medical Center, Orange. 1st Tuesday of each month, September-June, 7:30-9:00 p.m. Contact: Edward I. Miller, MD, 301 Newport Blvd., Newport Beach. (714) 645-8600.

Continuously—**Cytopathology Seminars.** UCSF. 2nd Thursday of each month, September-June. 5:00-6:00 p.m. Contact: Eileen King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously — **Cytopathology Tutorial Program.** UCSF. Courses may be arranged throughout the year on the basis of individual needs and goals; fees are prorated accordingly. Arrangements should be discussed with instructor, Eileen B. King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

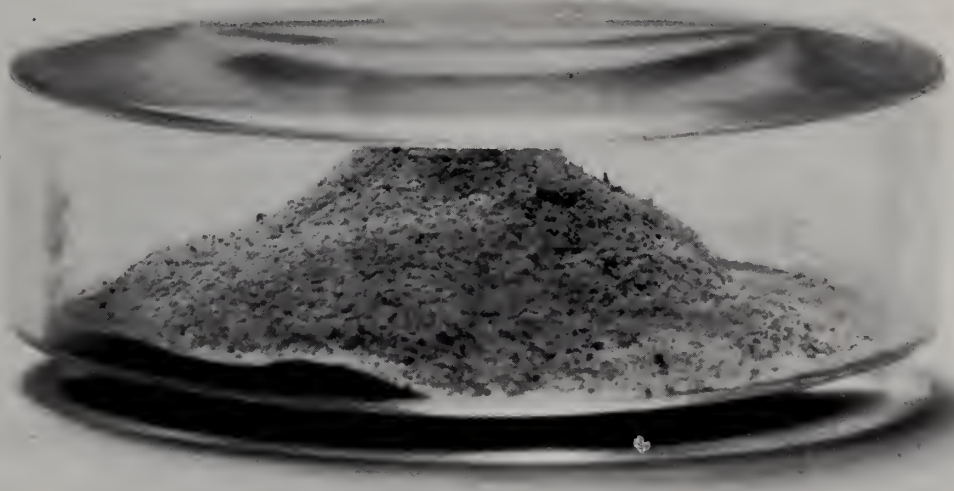
Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two-part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

(Continued on Page 48)

PROLOID® (thyroglobulin)
Caution: Federal law prohibits dispensing without prescription.
Description. Proloid (thyroglobulin) is obtained from a purified extract of frozen hog thyroid. It contains the known calorigenically active components, Sodium Levothyroxine (T_4) and Sodium Liothyronine (T_3). Proloid (thyroglobulin) conforms to the primary USP specifications for desiccated thyroid—for iodine based on chemical assay—and is also biologically assayed and standardized in animals.
Chromatographic analysis to standardize the Sodium Levothyroxine and Sodium Liothyronine content of Proloid (thyroglobulin) is routinely employed.
The ratio of T_4 and T_3 in Proloid (thyroglobulin is approximately 2.5 to 1.
Proloid (thyroglobulin) is stable when stored at usual room temperature.
Indications. Proloid (thyroglobulin) is thyroid replacement therapy for conditions of inadequate endogenous thyroid production: e.g., cretinism and myxedema. Replacement therapy will be effective only in manifestations of hypothyroidism.
In simple (nontoxic) goiter, Proloid (thyroglobulin) may be tried therapeutically, in nonemergency situations, in an attempt to reduce the size of such goiters.
Contraindication. Thyroid preparations are contraindicated in the presence of uncorrected adrenal insufficiency.
Warnings. Thyroglobulin should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 0.5 to 1.0 grain (32 to 64 mg) and increased by the same amount in increments at two-week intervals. This demands careful clinical judgment.
Morphologic hypogonadism and nephroses should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.
Myxedematous patients are very sensitive to thyroid and dosage should be started at a very low level and increased gradually.
Precaution. As with all thyroid preparations this drug will alter results of thyroid function tests.
Adverse Reactions. Overdosage or too rapid increase in dosage may result in signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.
Dosage and Administration. Optimal dosage is usually determined by the patient's clinical response. Confirmatory tests include BMR, T_3 ^{131}I resin sponge uptake, T_3 ^{131}I red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Clinical experience has shown that a normal PBI (3.5-8 mcg/100 ml) will be obtained in patients made clinically euthyroid when the content of T_4 and T_3 is adequate. Dosage should be started in small amounts and increased gradually with increments at intervals of one to two weeks. Usual maintenance dose is 0.5 to 3.0 grains (32 to 190 mg) daily.
Overdosage Symptoms. Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.
(Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)
How Supplied. ¼ grain; ½ grain; scored 1 grain; 1½ grain; scored 2 grain; 3 grain; and scored 5 grain tablets, in bottles of 100 and 1000.
Full information available on request.
WARNER/CHILCOTT
Division, Warner-Lambert Company
Morris Plains, New Jersey 07950
PR-GP-31-B/W

IN NATURAL THYROID THERAPY:

ARE PATIENTS GETTING THE POTENCY YOU PRESCRIBE?



Unlike U.S.P. desiccated thyroid, Proloid® (thyroglobulin) offers the assurance of constant potency.

To begin with, Proloid is uniquely purified. The thyroglobulin extracted from hog thyroid is devoid of any glandular debris.

Then, Proloid is chemically and biologically assayed to assure consistent metabolic activity from batch to batch. The T_4 and T_3 content of every dose is blended for optimal thyroid replacement.

Important, too, is the fact that Proloid is invariably "fresh" when your patients take it. Under proper storage conditions, its potency will not diminish for at least four years.

All of which adds up to this: the potency of Proloid is constant...for more consistent results.

PROLOID®
(thyroglobulin)

natural thyroid therapy that leaves nothing to chance

Opinion & Dialogue

Is there a need for a drug compendium?

Government Health Official

Henry E. Simmons, M.D.
Deputy Assistant Secretary for Health
Department of Health, Education and Welfare

A drug compendium of the type I envision would fill a definite need for the practicing physician. Such a compendium would give him all the information necessary for using a drug intelligently, and it would do so in a clear, concise, convenient, objective and balanced fashion.

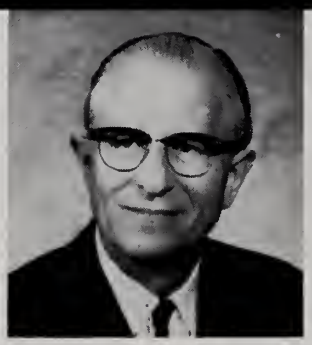
What a Compendium Should Contain

I believe the compendium should inform the doctor what a drug will do, when he should use i for what type of patient, for how long, in what dose, what benefits his patient is likely to obtain, the risks involved, and cross-reaction with other drugs.

The information would be based on the package insert and have the same legal status. In fac a complete compendium with cor plete and current information might even eliminate the necessi

Maker of Medicine

Joseph F. Sadusk, Jr., M.D.
Warner-Lambert Company



A drug compendium, or preferably compendia, should, I believe, be private, not federal, ir sponsorship. They should contair comprehensive listings of drugs available for prescribing. They should be single, legibly printed volumes of reasonable size, updated quarterly or semiannually and completely revised every yea

Function of a Compendium

A compendium should furnish the following information or drugs in the following order: indi tions for use, side effects, adver drug reactions, contraindication drug interactions, drug dosage a the dosage forms marketed. Dru prices should not be included be cause they vary so widely and change rapidly.

No compendium should se forth drugs of choice or discuss relative efficacy. Such question must be left for the practicing p sician to decide, whether on the basis of the medical literature, h own clinical experience, advice colleagues, information supplie by manufacturers, and so on.

Nor should a compendium undertake to educate the docto how to use drugs. Rather, it mu be a reference source designed marily to refresh his memory as drugs he may not use regularly.

r a package insert in many in-
ances. This would constitute a
bstantial saving for the manu-
cturer.

By a complete compendium,
lo not mean a volume of prohibi-
ve size. You don't need a book
escribing 25,000 products with
enormous amount of repetition.
ther, drugs should be arranged
class. Mutually applicable infor-
ation would be provided, along
th brief discussions pinpointing
ferences in specific drugs of
at class. Listings would be cross-
dexed in a useful way.

her Available Documents as urces of Information

Existing references such as
R and the AMA Drug Evaluation
obviously useful but they are
omplete. Either they are not
ss-referenced by generic name
d do not group drugs with simi-
characteristics, or they do not
all the available and legally
rketed drugs. And some of
se omitted may be very useful.

On the other hand, drugs made by more than one supplier, tetracycline for example, may be fully described a dozen times in the same book.

While perhaps PDR could be rearranged and cross-indexed with generics included, and while the AMA Drug Evaluation might also be modified and expanded, I am not sure that the end result would have all the attributes required for a useful compendium. At the same time, you would run the risk of amassing a voluminous and unwieldy tome.

Should Editorial Comments Accompany the Listings?

Subjective judgments, in my opinion, have no place in a compendium. However, if there is substantial evidence based on a sound body of science concerning relative efficacy of several drugs, certainly that information should be included. The committee of experts compiling and editing a particular section would also have to assess and indicate instances where a meaningful difference between drugs is pertinent.

Sponsorship, Compilation and Editing

Producing a book like this would undoubtedly be difficult and demanding. It would obviously take a great deal of talent and expertise, and would require a varied and experienced group, ranging from writers and editors to highly skilled clinicians and pharmacologists. Style, format and clarity of language would play an important part in determining the usefulness of the book. And it should be updated periodically and completely revised annually.

I have no opinion whether the government or the private sector should sponsor and/or finance the compendium. What is most important is that the compendium be an authoritative, objective and useful source of information for the doctor to have at hand as a ready reference.

---

uld in no way imply control over
h practitioner's prerogatives.

Wy Another Compendium?

A practicable, single-volume
cpendium cannot, nor is it
ecessary to, include all drugs on
h market today. From my prac-
ic of internal medicine for some
15 ears, my experience as a con-
sulant, and as a faculty member
of our or five medical schools, I
wold estimate that a doctor uses
on 30 to 35 drugs regularly. The
192 Physicians' Desk Reference,
ncdentally, contained about
2,50 entries.

As to whether there should be
a fderal compendium, in my opin-
or as stated earlier, the answer is
eas—there should *not* be one. The
prcosal assumes that existing
cpendia are inadequate. We're
not ure of that at all. Whatever its
mrfections, the present drug
nfmation system in the U.S. is
ope, multifaceted, pluralistic and
extnsive. Good compendia exist,
as ell as other ample sources on
dru therapy, ranging from journal
ite ture through AMA Drug Evalu-
atic to company materials. Not
il ysicians may use such
ouces as often or as well as they
ho d, but that is the fault of the
nal not of the sources.

In any event, rather than produce another book, it makes much more sense to work on improving existing compendia, and perhaps they could, as knowledge advances, include more accumulated clinical data and experience, and more information on drug interactions and adverse reactions.

Implications of a Federal Compendium

Take a hard look at the implications of a federal compendium. It would have the force of law, virtually dictating what drugs to use and how to use them. In effect, it would be a regulatory document with legal or quasi-legal status, posing medical/legal problems similar to those the doctor may now encounter if and when he departs from the provisions of the package insert. A compendium under federal aegis would tend to restrict decisions on drug therapy to one orthodox level—a most dangerous trend for medicine.

New Compendium—A Medical Option

I detect no ground swell of initiative or support whatsoever for a federal compendium—or, for that matter, for a new compendium of any type. A 1969 PMA survey conducted by Opinion Research Corporation found that only 15 per cent of those physicians interviewed felt a new compendium was needed. And a large majority did not favor the involvement of the federal government if one were to be created, preferring instead a nongovernmental consortium.

Even if we come to a time when the medical profession itself opts for a new kind of compendium, it should be handled and financed, ideally, outside both government and industry. Final review and editorial authority could be delegated, say, to specialty bodies and medical societies—but above all, *not* the government.

Surely the health care system in the United States has far more vital matters to consider than the extensive cost and effort that would have to go into the preparation and maintenance of a new, monolithic compendium, and especially one bearing the imprimatur of the federal government.

Opinion & Dialogue

What is your opinion, doctor? We would welcome your comments.

The Pharmaceutical
Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005

(Continued from Page 44)

Continuously—**Scintillation Camera Workshop.** UCSF. Workshops provided for physicians and nuclear medicine technologists by special arrangement, limited to 30 trainees per workshop. One- or two-day intensive training periods, basic instruction in scintillation camera theory, scintographic principles and scintiphotographic interpretations. $50. Contact: UCSF.

Continuously — **Scintiphotograph Interpretation.** UCSF and Nuclear Medicine Section, Department of Radiology, UCSF. By special arrangement, designed to furnish physicians with an opportunity to participate in the daily activities of a university laboratory. Two-week training period participation in daily interpretation conferences, correlation conferences, routine training conferences. $175. Contact: UCSF.

Grand Rounds—Radiology-Pathology

Mondays

Pathology. 1:00 p.m., Sacramento Medical Center, Sacramento. UCD.

Tuesdays

Radiology. 3rd Tuesday of each month, 8:00 a.m., Bothin Auditorium, Children's Hospital and Adult Medical Center, San Francisco.

SURGERY AND ANESTHESIOLOGY

May 17-18—**Eye Residents and Fellows of Northern California —4th Annual Meeting.** Letterman Gen. Hosp., San Francisco. Friday-Saturday. Contact: Allan Flach, MD, Chr., Dept. of Ophthalmology, UCSF.

May 18—**Surgical and Clinical Anatomy of the Vascular System.** International College of Surgeons, So. Calif. Division, at Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Darline Murphy, Ex. Sec., 136 N. Brighton, Burbank 91506. (213) 846-0669.

May 21-22—**Society for Surgery of the Alimentary Tract.** Hilton Hotel, San Francisco. Tuesday-Wednesday. Contact: Robert Zeppa, MD, Dept. of Surg., U. of Miami, Box 520875, Biscayne Annex, Miami 33152. (305) 350-6721.

May 23-25—**Cardiologists' Appraisal of Cardiac Surgery.** See Medicine, May 23-25.

May 30-June 2—**California Society of Anesthesiologists Inc.—Annual Scientific Meeting.** Sahara Tahoe Hotel, Lake Tahoe. Wednesday-Saturday. 15 hrs. Contact: Norman R. Catron, Ex. Sec., 100 S. Ellsworth Ave., Suite 400, San Mateo 94401. (415) 343-4644.

June 7—**Lumbar Laminectomy—A Critical Analysis.** St. Mary's Hospital, San Francisco. Friday. Contact: Walter J. Treanor, MD, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 668-1000, ext. 465.

June 8-9—**Orthopedic Medicine II—A Tribute to Cyriax.** St. Mary's Hospital, San Francisco. Saturday-Sunday. Contact: Walter J. Treanor, MD, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 668-1000, ext. 465.

June 9-13—**Pacific Coast Oto-Ophthalmological Society.** Hotel del Coronado, Coronado. Sunday-Thursday. $35 for members; $50, non-members. Contact: Daniel G. Vaughan, MD, Exec. Sec., Room 494U, UCSF, San Francisco 94143. (415) 666-1993.

June 12-16—**Barany Society.** Disneyland Hotel, Anaheim. Wednesday-Sunday. $200. The program of this international vestibular society will be devoted to the problem of Meniere's disease. Contact: Jack L. Pulec, MD, Otologic Medical Group, Inc., 2122 W. 3rd St., Los Angeles 90057.

June 15—**Orthopaedic Surgery and Surgical Anatomy of the Neck and Upper Extremity.** International College of Surgeons, So. Calif. Division, at L.A. Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Darline Murphy, Exec. Sec., 136 N. Brighton, Burbank 91506. (213) 486-0669.

June 15-16—**Techniques in Respiratory Therapy.** American Society of Anesthesiologists at St. Francis Hotel, San Francisco. Saturday-Sunday. 13 hrs. $75 for members; $100, non-members. Contact: ASA, 515 Busse Highway, Park Ridge, Ill. 60068. (312) 825-5586.

June 22—**Ophthalmology Clinical Conference.** STAN. Saturday.

June 27-28—**Highlights of Modern Ophthalmology.** PMC. Thursday-Friday. 16 hrs.

June 27-29—**Phaco-Emulsification.** St. John's Hospital and So. Calif. Lions Eye Institute at St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

July 1-Sept. 13—**Basic Science Course in Ophthalmology,** STAN. 6 wks.

July 11-13—**Laser Photocoagulation and Fluorescein Angiography.** Palo Alto Medical Clinic, Palo Alto. Thursday-Saturday. 20 hrs. $300. Contact: H. Christian Zweng, MD, Palo Alto Medical Clinic, 300 Homer Ave., Palo Alto 94301. (415) 321-4121.

July 25-27—**Phaco-Emulsification.** St. John's Hospital and Southern California Lions Eye Institute at St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

August 14-18—**Urology.** UCLA. Wednesday-Sunday.

September 26-28—**Phaco-Emulsification.** St. John's Hospital and Southern Calif. Lions Eye Institute at St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

September 26-28—**Cerebral Palsy—New Perspectives.** American Academy for Cerebral Palsy at Children's Hospital at Stanford. Thursday-Saturday. $75. Contact: E. E. Bleck, MD, Children's Hospital at Stanford, 520 Willow Rd., Palo Alto 94304.

Continuously—**Neurological Sciences.** St. Francis Hospital, Lynwood. Wednesdays, 7:30-8:30 a.m. Presentations of radiological evaluations and pathological specimens of current material and review of current topics in specialty. Weekly notification of cases available. Contact: Ralph Miller, Admin. Asst., St. Francis Hospital, 3630 Imperial Highway, Lynwood 90262. (213) 639-5111, ext. 365.

Continuously—**Basic Science Lecture Series.** Dept. of Surgery, St. Mary's Hospital, San Francisco. Mondays, 11:15 a.m.-12:15 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Mini Residencies in Orthopaedics.** STAN. Postgraduate traineeships of 4-14 days duration, as you wish. No tuition but donations accepted. Contact: Orthopaedic Division, Dept. of Surgery, Stanford.

Continuously—**Orthopedic Lecture Series.** Alternately at St. Mary's, St. Joseph's, Mary's Help, VA Martinez, Kaiser San Francisco, and Harkness Memorial Hospitals. Third Tuesday of each month, 6:00 p.m. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Orthopedic Trauma Conference.** USC at Los Angeles County-USC Medical Center. Mondays, 7:00-9:00 p.m. Contact: Dept. of Orthopedics, USC School of Med., 2025 Zonal Ave., Los Angeles 90033. (213) 225-3131.

Continuously—**Preceptorships in General Surgery.** UCSF. By arrangement.

Continuously—**Preceptorships in Neurological Surgery.** UCSF. By arrangement.

Continuously—**Preceptorships in Urology.** UCSF. By arrangement.

Continuously—**Training for Physicians in Nephrology.** CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Hemodialysis peritoneal dialysis, renal biopsy, and kidney transplantation 160 hrs. Contact: Stewart W. Shankel, MD, LLU.

Continuously—**Surgical Anatomy.** St. Mary's Hospital, San Francisco. Mondays, 4:30 p.m., St. Mary's Hall, 2 W. Classroom. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Cline Clinic.** St. Mary's Hospital, San Francisco. Mondays, 1:30 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Morbidity and Mortality Conference.** 4th Monday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Surgical Pathology Conference.** See Radiology/Pathology, Continuously.

Continuously—**Thoracic Surgery Conference.** San Joaquin General Hospital, Stockton. Fourth Wednesday of each month, 9:00-10:30 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Medical Surgical Combined Conference.** San Joaquin General Hospital, Stockton. Second Wednesday of each month, 10:00-11:15 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Orthopaedic Audio-Synopsis Foundation.** A nonprofit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

Grand Rounds—Surgery

Mondays

9-10 a.m., Morrissey Hall, St. Mary's Hosiptal, San Francisco.

Tuesdays

Orthopedic Surgery. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:00-10:00 a.m., San Joaquin General Hospital, Stockton.

1st and 3rd Wednesdays. 11:00 a.m., Auditorium, Brown Building, Mount Sinai Hospital, Los Angeles. UCLA.

3:30 p.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

Neurology and **Neurosurgery.** 11:00-12:15, Room 663, Science Building, UCSF.

Fridays

1:00-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego, UCSD.

Urology. 8:00 a.m., 3rd floor conference room, University Hospital of San Diego County, San Diego. UCSD.

Orthopedics. 8:00-9:00 a.m. St. Mary's Hospital, San Francisco.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA.

Orthopedics. 10:00 a.m. Auditorium of the Children's Division, Los Angeles County-USC Medical Center. The third Saturday of each month. USC.

OF INTEREST TO ALL PHYSICIANS

May 15—**Current Clinical Research — Spring Symposium.** STAN. Wednesday.

May 15—**Office Orthopedics.** Alameda-Contra Costa Chapter, Calif. Academy of Family Physicians, at Edgewater Hyatt House Hotel, Oakland. Wednesday. Contact: Gordon Benner, MD, 3000 Colby St., Berkeley. (415) 848-7533.

May 15—**Changing Patterns in the Practice of Medicine—Annual Medical Staff Symposium.** Memorial Hospital Medical Center of Long Beach. Wednesday. Contact: H. David Mosier, MD, Prog. Comm. Chrm., Memorial Hosp. Med. Ctr., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3236.

May 18—**Symposium on Hypertension and Stroke.** Western Division, American Geriatrics Society at Palm Springs. Sunday. 6 hrs. $25. Contact: Richard M. Johnson, MD, Sec., Western Div., American Geriatrics Soc., 211 Cherry Ave., Long Beach 90802.

May 18—**Utilization Review in Hospitalized Patients.** UCSF at St. Francis Hospital, San Francisco. Saturday.

May 30-June 1—**American College of Emergency Physicians, California Chapter—3rd Annual Scientific Assembly.** Fairmont Hotel, San Francisco. Thursday-Saturday. 16 hrs. Contact: Karl G. Mangold, MD, 897 MacArthur Blvd., Suite 101, San Leandro 94577. (415) 638-3979.

June 1.—**Symposium on Hypertension and Stroke.** Western Division, American Geriatrics Society at Long Beach. Saturday. 6 hrs. $25. Contact: Richard M. Johnson, MD, Sec., Western Div., American Geriatrics Soc., 211 Cherry Ave., Long Beach 90802.

June 6—**Drug Therapy and Pharmacy.** USC. Thursday.

June 12—**The Impotent Male and the Liberated Female.** See Psychiatry, June 12.

June 15—**Nutrition and the Physician.** UCLA. Saturday.

June 16-20—**1974 Birth Defects Conference.** See Pediatrics, June 16-20.

July 3-6—**Sexual Dysfunction.** UCLA at Residential Conference Center, Lake Arrowhead. Wednesday-Saturday.

July 14-20—**Management Seminar for University/College Health Services.** California Polytechnic State Univ., San Luis Obispo. Sunday-Saturday. $125. Contact: Mr. David Graham, Health Center, Calif. Polytechnic State Univ., San Luis Obispo 93407.

August 17-28—**Postgraduate Refresher Course—17th Annual.** USC at Hawaii. 12 days. $225.

August 21-24—**Family Practice Board Review.** UCLA at Beverly Hilton Hotel, Los Angeles. Wednesday-Saturday.

August 25-30—**Family Practice Refresher Course.** UCD at Squaw Valley. Sunday-Friday.

September 3-8—**Family Practice Review Course—5th Annual.** UCI. Tuesday-Sunday. 44 hrs.

September 11-14—**Life Saving Measures for the Critically Injured.** UCLA. Wednesday-Saturday.

September 21-22—**Acupuncture.** UCLA. Saturday-Sunday.

Continuously—**Continuing Medical Education Noon Conferences.** The Hospital of the Good Samaritan, Los Angeles. Every weekday, 12-1 p.m. For monthly calendar, contact: Janie Sternal, Coord., Cont. Med. Ed., Hosp. of the Good Samaritan, 1212 Shatto St., Los Angeles 90029. (213) 482-8111.

Continuously—**Clinical Problems in Daily Practice: Physiological Basis and Practical Management.** UCSF at Chinese Hospital, San Francisco. 1st Tuesday of each month; 8:00-9:30 p.m. May—A Critical Overview of Antibiotic Therapy; June—The Patient in Respiratory Failure; July—Diabetes Mellitus; Aug.—Congestive Heart Failure; Sept.—Jaundice; Oct. & Nov.—to be announced.

Continuously—**Clinical Conferences.** UCSF and Community Hospital of Santa Cruz at Community Hospital, Santa Cruz. 2nd Wednesday of each month, Oct. 10, 1973-June 12, 1974, 11:00 a.m.-2:30 p.m. 27 hours. $50 for series; $7.50 per lecture. May—Clinic on Obesity; June—The Impotent Male and the Liberated Female.

Continuously—**Bedside Clinics.** See Medicine, Continuously.

Continuously—**Family Health Program—Southern California.** 2925 N. Palo Verde, Long Beach. Second Friday of each month. 1:00-2:00 p.m. Contact: UCI.

Continuously — **Lecture Program.** Riverside-San Bernardino Chapter, American Academy of Family Physicians and UCI at Ram's Horn Inn, San Bernardino. 3rd Thursday of each month. 7:30 p.m. Contact: UCI.

Continuously—**Lecture Program.** UCI and Orange County Chapter, American Academy of Family Physicians at Saddleback Inn, Santa Ana. 2nd Monday of each month, 7:30 p.m. Contact: UCI.

Continuously—**Hospital Lecture Program.** UCI at Anaheim Mem. Hosp.; Brea Comm. Hosp.; Fountain Valley Comm. Hosp.; Garden Park Gen. Hosp., Anaheim; Hartland Comm. Hosp., Baldwin Park; Huntington Intercomm. Hosp., Huntington Beach; Imperial Gen. Hosp., Inglewood; La Habra Comm. Hosp.; La Mirada Comm. Hosp.; La Palma Intercommunity Hosp., La Palma; Los Alamitos Gen. Hosp.; Mission Comm. Hosp., Mission Viejo; Palm Harbor Hosp., Garden Grove; Riviera Hosp., Torrance; Rio Hondo Mem. Hosp., Downey; San Gabriel Valley Comm. Hosp., San Gabriel; Stanton Comm. Hosp.; Studebaker Comm. Hosp., Norwalk; West Anaheim Gen. Hosp.; Westminster Comm. Hosp. Contact: UCI.

Continuously—**Professional Education Program.** Porterville State Hospital. Contact: Frank McCarry, MD, P.O. Box 2000, Porterville. (209) 784-2000.

Continuously—**Round Tables with Pacific Medical Center.** PMC and Sonoma Valley Hospital at Sonoma Valley Hospital, Sonoma. Second Monday of each month in Dining Room of the hospital, 8:00-10:00 p.m. $100 per series, $15 per session. Contact: William J. Newman, MD, P.O. Box B, Sonoma 95476. (707) 996-3621.

Continuously—**Basic Science Lecture Series.** UCSD Mondays, 4:00 p.m., third floor conference room, University Hospital of San Diego County, San Diego. Contact: UCSD.

Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $75 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

Continuously—**Medical Media Network.** Programs and study guides produced in association with faculties of major medical schools and centers throughout the U.S. MMN administered by University Extension, UCLA. Rental or purchase, 16 mm, super 8 mm, videotape and video-cassette. Provides physicians with current educational programs. Contact: Ms. Jan MacAllister, Distribution Mgr., MMN, 10995 Le Conte Ave., Room 540, Los Angeles 90024. (213) 825-7781.

Continuously—**Stanford-Mills Memorial Hospital Continuing Education Program.** STAN at Mills Memorial Hospital, San Mateo. Tuesday-Friday weekly. Basic Science for the Clinician, Grand Rounds, Intensive Care. Contact: STAN.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

FAMILY PRACTICE

May 31, June 1-2—**Physicians Institute.** Inn of the Seventh Mountain, Bend. Contact: Robert Taubman, MD, 2153 S.W. Main St., Portland 97205. 20 Category I credits OAFP and OMA.

June 8—**Infection in Medical Practice.** Jantzen Beach Thunderbird, Portland, 8:00 a.m. Contact: Ron Jones, MD, The Permanente Clinic, 5055 N. Greeley, Portland 97217. 6 Category II credits OAFP and OMA.

INTERNAL MEDICINE

May 25-26—**Oregon Society of Internal Medicine Annual Scientific Program.** Kah-Nee-Ta Lodge, Warm Springs. 9:00 a.m. to 12:00 p.m. and 9:00 a.m. to 2:00 p.m. Contact: C. Carter Boggs, MD, 600 Harriman, Bend 97701. 8 Category II hours OAFP and OMA.

MEDICINE

May 15-17—**Combined American College of Emergency Physicians, Emergency Department Nurses Association, and Emergency Medical Technicians.** Contact: Donald L. McNeill, MD, Good Samaritan Hospital, 1015 N.W. 22nd, Portland 97210.

May 15, 16, 17—**Medical and Surgical Emergencies.** Klamath Falls, Medford and Roseburg. Contact: Circuit Course Program, Oregon Medical Association, 2164 S.W. Park Place, Portland 97205. 4 Category I credits OAFP and OMA.

May 23—**Symposium on Prostaglandin.** University of Oregon Medical School, 3181 S.W. Sam Jackson Park Road, Portland 97201. Contact: M. Roberts Grover, Jr., MD, Associate Dean, University of Oregon Medical School, (503) 225-8228.

May 29—**Traumatic Emergencies.** Salem Memorial Hospital, Salem. 1:30 p.m. Contact: Circuit Course Program, Oregon Medical Association, 2164 S.W. Park Place, Portland 97205. 4 Category I credits OAFP and OMA.

May 31—**Trauma in Children.** Sacred Heart General Hospital Auditorium, Eugene. Contact: Kenneth Singer, MD, 750 E. 11th Avenue, Eugene 97401. 7½ Category I credits OAFP and OMA.

PEDIATRICS

May 22-23—**Pediatric and OB Emergencies.** Newport and Coos Bay. Contact: Circuit Course Program, Oregon Medical Association, 2164 S.W. Park Place, Portland 97205. 4 Category I credits OAFP and OMA.

MEDICAL GRAND ROUNDS

May 21—7:00 p.m.—Providence Hospital, Portland—Consequences and Cures of the Use of Prescription Drugs.

WASHINGTON, MONTANA and ALASKA

REGIONAL MEDICAL PROGRAM

THIS LISTING of continuing medical education activities in Washington, Montana, and Alaska is supplied by Washington/Alaska Regional Medical Program. In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

May 12-16—**American Association of Plastic Surgeons.** Olympic Hotel, Seattle. Sunday-Thursday. Contact: Maurice J. Jurkiewicz, Emory University Affiliated Hospital, 69 Butler St., S.W., Atlanta, Georgia 30303.

May 15-17—**Advances in Internal Medicine.** Wednesday-Friday. Health Sciences. 18 hrs. $150. Contact: Richard L. Reimer, Asst. Dir., E-305 HSB, SC-50, Univ. of Wash. Sch. of Med., Seattle 98195. (206) 543-1050.

May 16-17—**Pediatric Care for Family Practitioners and Pediatricians.** Thursday-Friday. 13 hrs. $35. Contact: William O. Robertson, Children's Orthopedic Hospital, 4800 Sandpoint Way, Seattle 98105. (206) 634-5072.

May 17-18—**Problems in Gastrointestinal Surgery.** Friday-Saturday. Virginia Mason Medical Center Auditorium. 9 hrs. $35. Contact: Kenneth Wilske, MD, Dir., CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA3-3700 ext. 470.

May 24-25—**Hypertension: Etiology and Factors in Choice of Drugs.** Friday-Saturday. Virginia Mason Clinic Medical Center Auditorium. 13 hrs. $50. Contact: Kenneth Wilske, MD., Dir. CME, Virginia Mason Clinic Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA3-3700 ext. 470.

May 30-June 1—**Washington Academy of Family Physicians Annual Meeting.** Holiday Inn, Spokane. Thursday-Saturday. Contact: John P. Plastino, MD, 6th Ave. Medical Bldg., Spokane 99204.

June 7-8—**Interpretation of Liver Biopsies.** Friday-Saturday. Virginia Mason Medical Center Auditorium. 9 hrs. $50. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA3-3700 ext. 470.

June 12-August 28—**Expo '74—Topics in Medicine.** Every Wednesday morning for 12 weeks. Deaconess Hospital, Spokane. 3 hrs. per session. $10 per session; $90 for 12 sessions. Contact Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305, HSB, SC-50, Seattle 98195. (206) 543-1050.

June 28-29—**Diagnosis and Management of Diffuse Pulmonary Infiltrates.** Friday-Saturday. Virginia Mason Medical Center Auditorium. 9 hrs. $35. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA3-3700 ext. 470.

July 14-20—**Radiation Research Society, 22nd Annual Meeting.** Sunday-Saturday. Contact: R. J. Burk, Jr., 4211 39th St. NW, Washington, D.C. 20016.

July 25-27—**American Electroencephalographic Society.** Thursday-Saturday. Washington Plaza, Seattle. Contact: Mrs. Margaret H. Henry, 36391 Maple Grove Rd., Willoughby Hills, Ohio 44094.

July 29-31—**World of the Heart and Lung.** Monday-Wednesday. Seattle. Fee not set. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305, HSB, SC-50, Seattle 98195. (206) 543-1050.

Index to The Western Journal of Medicine Advertising

Bank of America 29

Breon Laboratories, Inc.
Bronkotabs 16

Burroughs Wellcome Co.
Empirin Compound/Codeine 25

Classified 26, 33

Compton Foundation 26

Dorsey Laboratories
Triaminic Expectorant 9

Geigy Pharmaceuticals
Tofranil-PM 10, 11, 12

Lakeside Laboratories, Inc
Norpramin 17, 18

Eli Lilly & Company
Darvocet-N 24

Lake Forest Glen 31

Marion Laboratories, Inc.
Nico-400 ..... 38, 39

McNeil Laboratories
Parafone Forte 30, 31

Mead Johnson Laboratories
Quibron Plus 36, 37
Vasodilan ..... Back Cover

Medi-Fund Financial Corp 33

Merck Sharp & Dohme
Triavil 20, 21, 22

Pharmaceutical Manufacturers Association
Prescription Ads 46, 47

Presto Food Products, Inc.
Mocha Mix 19

A. H. Robins Co.
Donnatal/Albee with C 27, 28

Roche Laboratories
Dalmane ..... 2nd Cover and Page 1
Efudex 14, 15
Bactrim 40, 41, 42

Roerig (Pfizer)
Emete-Con 5, 6, 7, 8

G. D. Searle & Co.
Pro-Banthine ..... 52 and 3rd Cover

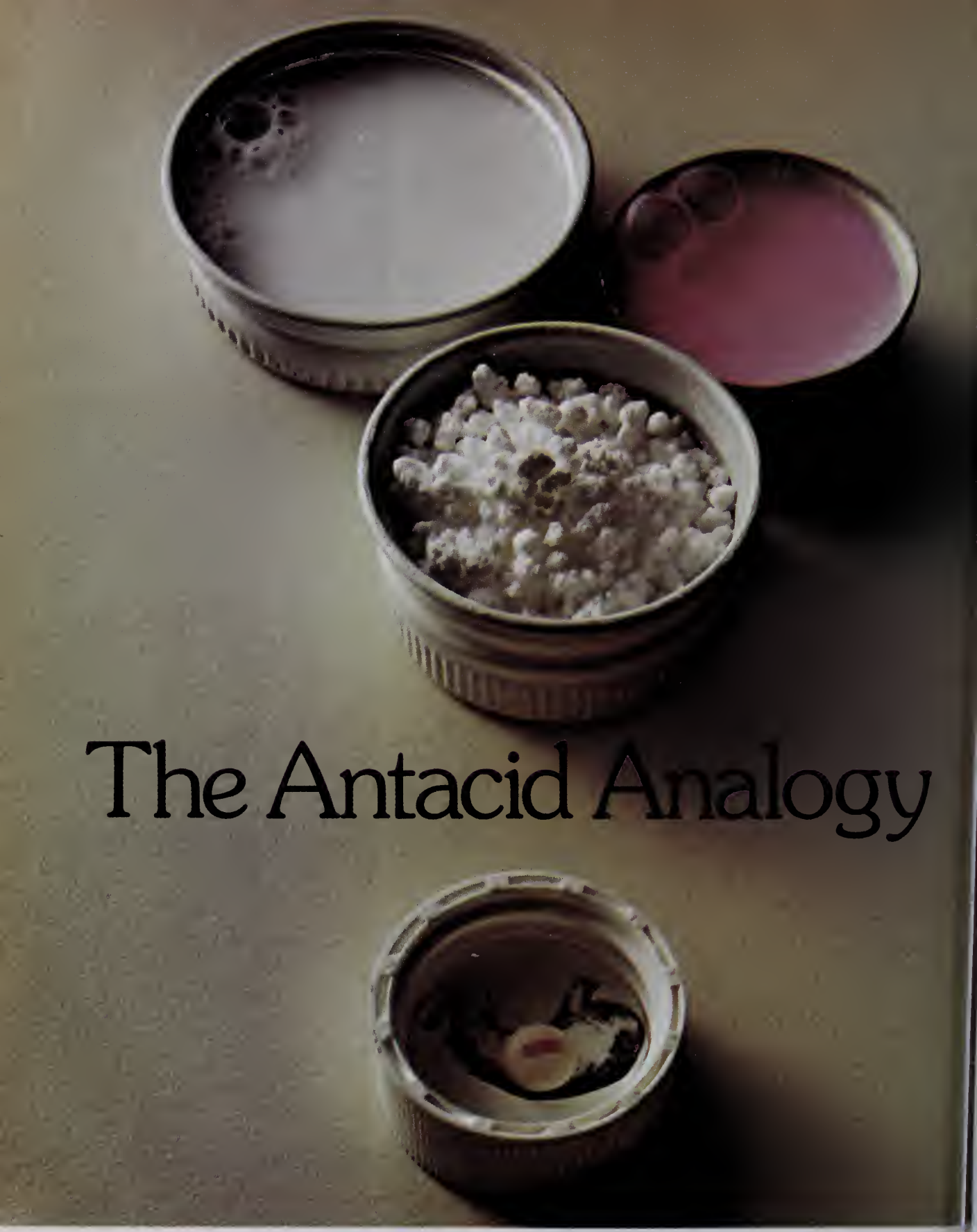
Security Pacific Bank 23

State Compensation Insurance Fund 32

United States Air Force
Medical Placement Office 13

Warner-Chilcott Laboratories
Proloid 44, 45

Wyeth Laboratories
Bicillin/Wycillin 2, 3



Indications: Pro-Banthine is effective as adjunctive therapy in the treatment of peptic ulcer. Dosage must be adjusted to the individual.

Contraindications: Glaucoma, obstructive disease of the gastrointestinal tract, obstructive uropathy, intestinal atony, toxic megacolon, hiatal hernia associated with reflux esophagitis, or unstable cardiovascular adjustment in acute hemorrhage.

Warnings: Patients with severe cardiac disease should be given this medication with caution.

Fever and possibly heat stroke may occur due to anhidrosis.

In theory a curare-like action may occur, with loss of voluntary muscle control. For such patients prompt and continuing artificial respiratio should be applied until the drug effect has been exhausted.

Diarrhea in an ileostomy patient may indicate obstruction, and th possibility should be considered before administering Pro-Banthine.

Precautions: Since varying degrees of urinary hesitancy may be evidenc by elderly males with prostatic hypertrophy, such patients should b advised to micturate at the time of taking the medication.

Overdosage should be avoided in patients severely ill with ulcerati colitis.

Adverse Reactions: Varying degrees of drying of salivary secretions m

Therapeutic comparisons in peptic ulcer.

Antacids have only one mode of action to relieve ulcer pain...

Pro-Banthine® has four.

brand of
propantheline bromide

Antacids:

Antacids relieve ulcer pain by neutralizing gastric acid. This action is relatively short-lived and they have no other mode of action.

Pro-Banthine:

Pro-Banthine suppresses gastric acid secretion. The antisecretory properties of Pro-Banthine are well established. By effectively blocking vagotonic impulses Pro-Banthine suppresses gastric secretion to reduce both total and free acid.

Pro-Banthine helps relieve pain. Pro-Banthine relieves ulcer pain by reducing gastric secretion and the motility and spasm of the gastrointestinal tract.

Pro-Banthine reduces acidity without subsequent acid rebound. The capacity of Pro-Banthine to reduce the secretion of total and free acid in the stomach has been demonstrated in scores of studies. None has demonstrated any significant evidence of acid rebound.

Pro-Banthine activity lasts about six hours. The effect of a single therapeutic dose (15 mg.) of Pro-Banthine lasts about six hours.* Pro-Banthine P.A.®, the prolonged-acting form, is active from 8 to 12 hours. Thus Pro-Banthine may be used to suppress acid, spasm, and pain around the clock, even during the sleeping hours when antacids, to be effective, must be taken almost hourly.

*Innes, I. R., and Nickerson, M., in Goodman, L. S., and Gilman, A. (editors): The Pharmacological Basis of Therapeutics, ed. 4, New York, The Macmillan Company, 1970, p. 537.

Pro-Banthine complements and enhances the action of antacids.

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Address medical inquiries to: G. D. Searle & Co.
Medical Department, Box 5110, Chicago, Ill. 60680

ccur as well as mydriasis and blurred vision. In addition the following dverse reactions have been reported: nervousness, drowsiness, dizziness, nsomnia, headache, loss of the sense of taste, nausea, vomiting, constipa-ion, impotence and allergic dermatitis.

Dosage and Administration: The recommended daily dosage for adult ral therapy is one 15-mg. tablet with meals and two at bedtime. Subse-quent adjustment to the patient's requirements and tolerance must be nade.

Pro-Banthine P.A.—Each tablet of Pro-Banthine P.A. (propantheline romide) contains 30 mg. of the drug in the form of sustained-release or timed-release beads; on ingestion about half of the drug is released within an hour and the remainder continuously as earlier increments are metabolized. Thus the result is even, high-level anticholinergic activity maintained all day and all night in most patients with only two tablets daily. Some patients may require one tablet every eight hours.

The contraindications and precautions applicable to Pro-Banthine 15 mg. should be observed.

How Supplied: Pro-Banthine is supplied as tablets of 15 and 7.5 mg., as prolonged-acting tablets of 30 mg. and, for parenteral use, as serum-type vials of 30 mg.

Must vasodilators and therapy for other diseases come into conflict?

not if the vasodilator is

VASODILAN®

(ISOXSUPRINE HCl)

the compatible vasodilator... no treatment conflicts reported

The cerebral or peripheral vascular disease patient often has coexisting disease[1] which calls for another drug along with his vasodilator. It may be a hypoglycemic, miotic, antihypertensive, diuretic, anticoagulant, corticosteroid, or coronary vasodilator.

Vasodilan is not incompatible with any of these drugs—no treatment conflict has been reported. And, unlike other vasodilators, Vasodilan has not been reported to affect carbohydrate metabolism, liver function, or intraocular pressure—or to complicate treatment of diabetes, hypertension, peptic ulcer, glaucoma, or liver disease.

In fact, there are no known contraindications to the use of Vasodilan in recommended oral doses, other than that it should not be given in the presence of frank arterial bleeding or immediately postpartum.

1. Gertler, M. M., et al.: Geriatrics *25*:134-148 (May) 1970.

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.
3. Threatened abortion.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.

Dosage and Administration: 10 to 20 mg. three or four times daily.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Adverse Reactions: On rare occasions, oral administration of the drug has been associated in time with the occurrence of severe rash. When rash appears, the drug should be discontinued. Occasional overdosage effects such as transient palpitation or dizziness are usually controlled by reducing the dose.

Supplied: Tablets, 10 mg.—bottles of 100, 1000, 5000 and Unit Dose; 20 mg.—bottles of 100, 500 and Unit Dose.

© 1973 MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA 47721 U.S.A. 734017

Mead Johnson LABORATORIES

THE WESTERN Journal of Medicine

VOLUME 120 • NUMBER 6 **JUNE 1974**

441 *Diagnosis of "Rheumatoid Variants"—Ankylosing Spondylitis, the Arthritides of Gastrointestinal Diseases and Psoriasis, and Reiter's Syndrome*
MICHAEL D. REYNOLDS, MD, and THOMAS J. RANKIN, MD

448 *Skeletal Scintigraphy—The Use of Technetium 99M-Labeled Complexes in the Detection of Early Osseous Involvement by Metastatic Tumors*
G. BRUCE HOPKINS, MD, KAI A. B. KRISTENSEN, MD, and CHARLES G. CAMPBELL, MD

452 *Gonococcal Antibiotic Resistance in Los Angeles* THOMAS F. KEYS, MD

SPECIALTY CONFERENCE
456 *Gonococcal Infections—Laboratory, Clinical and Epidemiological Aspects*
Moderator: BASCOM F. ANTHONY, MD; Discussants: THOMAS F. KEYS, MD, JAMES S. LOUIE, MD, and ROBERT N. YOSHIMORI, PhD
Teaching Conference in Infectious Diseases, UCLA School of Medicine, Harbor General Hospital, Torrance

MEDICAL PROGRESS
463 *Recent Advances in the Pathophysiology of Asthma*
ARCHIE F. WILSON, MD, PhD, and STANLEY P, GALANT, MD

MEDICAL STAFF CONFERENCE
471 *Immunoglobulin Deficiency Disorders* Discussion by DANIEL STITES, MD

476 IMPORTANT ADVANCES IN CLINICAL MEDICINE—*Neurology*

484 EDITORIALS • *The Rule of Wal* • *Immmunity to Reinfection in Patients with Gonorrhea* • *Instant Acupuncture for Nevada* • *Recent Advances in the Pathophysiology of Asthma*

CASE REPORTS
491 *Hyperthyroidism in the Presence of Panhypopituitarism—Thyroid Crisis and Hypothyroidism Following Radioiodine Treatment* G. T. KRISHNAMURTHY, MB, MS, and W. H. BLAHD, MD

497 *Treatment of a Cutaneous Nocardia Asteroides Infection with Minocycline Hydrochloride*
ERVIN EPSTEIN, MD

500 LETTERS TO THE EDITOR

TRAUMA ROUNDS
502 *Indications for Laparotomy Following Blunt Abdominal Injury*
Chief Discussant: F. WILLIAM BLAISDELL, MD; Editors: DONALD D. TRUNKEY, MD, and F. WILLIAM BLAISDELL, MD

GOVERNMENT AND MEDICINE
507 *Acupuncture in Nevada* WILLIAM M. EDWARDS, JR., MD, MPH

INFORMED OPINION
513 *Research in Medical Schools—A Personal View* SAMUEL I. RAPAPORT, MD

518 *In Memoriam*

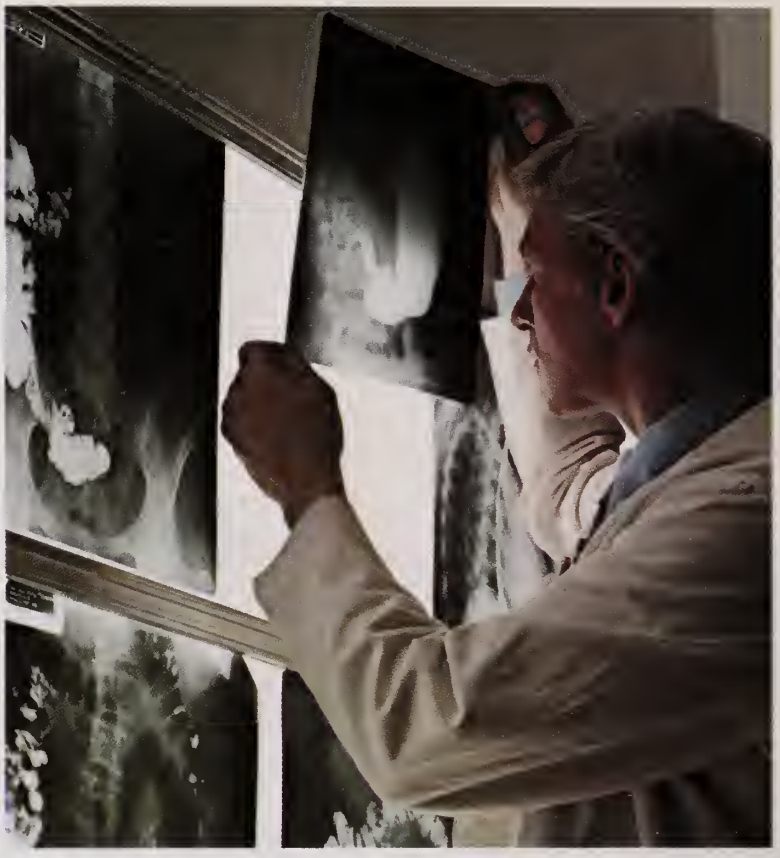
520 *Book Reviews*

521 *Volume Index*

★ **CONTINUING MEDICAL EDUCATION ACTIVITIES IN CALIFORNIA AND HAWAII; OREGON; WASHINGTON MONTANA, ALASKA, AND IDAHO**
(See Advertising Page 37)

MA 02115
10 SH
01%-EXC 052974 SUB05002010
NEW ENG JRL MED

When G.I. complaints occur in the absence of organic findings, underlying anxiety may be one factor



The influence of anxiety on gastrointestinal function. Excessive anxiety and tension can adversely affect the function of any portion of the gastrointestinal system. Complaints are varied, *e.g.*, epigastric pressure, heartburn, ulcer-like pain, diarrhea, etc. A vicious circle may develop in which anxiety and G.I. disorders intensify each other.

Prime objectives of total patient therapy include: symptomatic relief, removal of apprehensions about organic disease and helping the patient understand how excessive anxiety may trigger physical

---

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions

complaints. Brief counseling and the utilization of favorable factors in the patient's personality and environment can often provide needed support.

Antianxiety therapy. Antianxiety medication may prove a valuable supplement when counseling and reassurance are not sufficient to allay the patient's emotional distress and relieve his anxiety-provoked physical complaints. The agent prescribed should be both clinically effective and generally free from undesirable side effects. Librium (chlordiazepoxide HCl) meets these requirements with a high degree of consistency, and has a wide margin of safety and an excellent record of patient acceptance.

Whenever anxiety is a clinically significant factor, adjunctive Librium is used concomitantly with specific gastrointestinal drugs such as anticholinergic agents. Once anxiety has been reduced to appropriate levels, treatment with Librium should be discontinued.

For relief of excessive anxiety adjunctive

Librium® 10 mg

(chlordiazepoxide HCl)

1 or 2 capsules t.i.d./q.i.d.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

---

in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Supplied: Librium® Capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Libritabs® Tablets containing 5 mg, 10 mg or 25 mg chlordiazepoxide.

Opinion & Dialogue

Is there a need for a drug compendium?

A drug compendiu of the type I envision would fill a definite need for the practi ing physician. Such compendium wou give him all th information nec essary for usi a drug intelligently, and it would do so in a clear, concise, convenient, objective and balanced fashion.

What a Compendium Should Contain

I believe the compendium should inform the doctor what a drug will do, when he should use for what type of patient, for how long, in what dose, what benefits his patient is likely to obtain, the risks involved, and cross-reactio with other drugs.

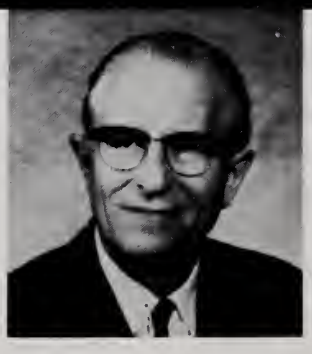
The information would be based on the package insert and have the same legal status. In fa a complete compendium with co plete and current information might even eliminate the necess

Government Health Official

Henry E. Simmons, M.D.
Deputy Assistant Secretary for Health
Department of Health, Education and Welfare

Maker of Medicine

Joseph F. Sadusk, Jr., M.D.
Warner-Lambert Company



A drug compendium, or preferably compendia, should, I believe, be private, not federal, sponsorship. They should conta comprehensive listings of drugs available for prescribing. They should be single, legibly printed volumes of reasonable size, updated quarterly or semiannually and completely revised every ye

Function of a Compendium

A compendium should fur nish the following information c drugs in the following order: ind tions for use, side effects, adve drug reactions, contraindicatio drug interactions, drug dosage the dosage forms marketed. Dr prices should not be included b cause they vary so widely and change rapidly.

No compendium should s forth drugs of choice or discuss relative efficacy. Such questior must be left for the practicing p sician to decide, whether on the basis of the medical literature, own clinical experience, advice colleagues, information suppli by manufacturers, and so on.

Nor should a compendiun undertake to educate the doctc how to use drugs. Rather, it mu be a reference source designec marily to refresh his memory a drugs he may not use regularly

r a package insert in many in-
ances. This would constitute a
ıbstantial saving for the manu-
cturer.

By a complete compendium,
lo not mean a volume of prohibi-
/e size. You don't need a book
escribing 25,000 products with
enormous amount of repetition.
ather, drugs should be arranged
class. Mutually applicable infor-
ation would be provided, along
th brief discussions pinpointing
ferences in specific drugs of
at class. Listings would be cross-
dexed in a useful way.

**her Available Documents as
urces of Information**

Existing references such as
R and the AMA Drug Evaluation
e obviously useful but they are
omplete. Either they are not
ss-referenced by generic name
d do not group drugs with simi-
characteristics, or they do not
all the available and legally
rketed drugs. And some of
se omitted may be very useful.

On the other hand, drugs made by more than one supplier, tetracycline for example, may be fully described a dozen times in the same book.

While perhaps PDR could be rearranged and cross-indexed with generics included, and while the AMA Drug Evaluation might also be modified and expanded, I am not sure that the end result would have all the attributes required for a useful compendium. At the same time, you would run the risk of amassing a voluminous and unwieldy tome.

Should Editorial Comments Accompany the Listings?

Subjective judgments, in my opinion, have no place in a compendium. However, if there is substantial evidence based on a sound body of science concerning relative efficacy of several drugs, certainly that information should be included. The committee of experts compiling and editing a particular section would also have to assess and indicate instances where a meaningful difference between drugs is pertinent.

Sponsorship, Compilation and Editing

Producing a book like this would undoubtedly be difficult and demanding. It would obviously take a great deal of talent and expertise, and would require a varied and experienced group, ranging from writers and editors to highly skilled clinicians and pharmacologists. Style, format and clarity of language would play an important part in determining the usefulness of the book. And it should be updated periodically and completely revised annually.

I have no opinion whether the government or the private sector should sponsor and/or finance the compendium. What is most important is that the compendium be an authoritative, objective and useful source of information for the doctor to have at hand as a ready reference.

---

ould in no way imply control over
practitioner's prerogatives.

y Another Compendium?

A practicable, single-volume
mpendium cannot, nor is it
cessary to, include all drugs on
market today. From my prac-
of internal medicine for some
years, my experience as a con-
ant, and as a faculty member
our or five medical schools, I
uld estimate that a doctor uses
30 to 35 drugs regularly. The
2 Physicians' Desk Reference,
dentally, contained about
00 entries.

As to whether there should be
deral compendium, in my opin-
as stated earlier, the answer is
—there should *not* be one. The
posal assumes that existing
pendia are inadequate. We're
sure of that at all. Whatever its
erfections, the present drug
rmation system in the U.S. is
n, multifaceted, pluralistic and
nsive. Good compendia exist,
ell as other ample sources on
therapy, ranging from journal
ature through AMA Drug Evalu-
n to company materials. Not
hysicians may use such
ces as often or as well as they
ld, but that is the fault of the
, not of the sources.

In any event, rather than produce another book, it makes much more sense to work on improving existing compendia, and perhaps they could, as knowledge advances, include more accumulated clinical data and experience, and more information on drug interactions and adverse reactions.

Implications of a Federal Compendium

Take a hard look at the implications of a federal compendium. It would have the force of law, virtually dictating what drugs to use and how to use them. In effect, it would be a regulatory document with legal or quasi-legal status, posing medical/legal problems similar to those the doctor may now encounter if and when he departs from the provisions of the package insert. A compendium under federal aegis would tend to restrict decisions on drug therapy to one orthodox level—a most dangerous trend for medicine.

New Compendium—A Medical Option

I detect no ground swell of initiative or support whatsoever for a federal compendium—or, for that matter, for a new compendium of any type. A 1969 PMA survey conducted by Opinion Research Corporation found that only 15 per cent of those physicians interviewed felt a new compendium was needed. And a large majority did not favor the involvement of the federal government if one were to be created, preferring instead a nongovernmental consortium.

Even if we come to a time when the medical profession itself opts for a new kind of compendium, it should be handled and financed, ideally, outside both government and industry. Final review and editorial authority could be delegated, say, to specialty bodies and medical societies—but above all, *not* the government.

Surely the health care system in the United States has far more vital matters to consider than the extensive cost and effort that would have to go into the preparation and maintenance of a new, monolithic compendium, and especially one bearing the imprimatur of the federal government.

Opinion & Dialogue

What is your opinion, doctor? We would welcome your comments.

The Pharmaceutical
Manufacturers Association
1155 Fifteenth Street, N.W.
Washington, D.C. 20005

THE WESTERN Journal of Medicine

Since 1902 • Formerly California Medicine

OWNED AND PUBLISHED BY THE CALIFORNIA MEDICAL ASSOCIATION
731 MARKET ST. • SAN FRANCISCO, CA 94103 • TELEPHONE (415) 777-2000

editorial communications to:
MALCOLM S. M. WATTS, M.D., *Editor*

business communications to:
LYTTON O. HETLAND, *Business Manager*

. . .

LLOYD H. SMITH, JR., M.D., *Associate Editor*
ROBERT F. EDWARDS, *Managing Editor*
DAVID GREER, *Associate Managing Editor*

Editorial Board

Chairman of the Board
Malcolm S. M. Watts, San Francisco

Allergy
Norman Shure, Los Angeles
Abba I. Terr, San Francisco

Anesthesiology
Ronald L. Katz, Los Angeles

Dermatology
George F. Odland, Seattle
Rees B. Rees, San Francisco
Richard B. Stoughton, La Jolla

General and Family Practice
Robert L. Hippen, San Diego
Herbert A. Holden, San Leandro

General Surgery
Frederick M. Anderson, Reno
Richard E. Gardner, San Francisco
Lucius D. Hill, Seattle

Industrial Medicine and Toxicology
Thomas H. Milby, Berkeley

Internal Medicine
Robert J. Bolt, Davis
J. David Bristow, Portland
Marcus A. Krupp, Palo Alto
Robert G. Petersdorf, Seattle
Donald W. Petit, Los Angeles
Edgar Wayburn, San Francisco
Nathan J. Zvaifler, San Diego

Neurology
Pierre M. Dreyfus, Davis
Robert A. Fishman, San Francisco
Phillip D. Swanson, Seattle

Obstetrics and Gynecology
Ralph C. Benson, Portland
William J. Dignam, Los Angeles
Ernest W. Page, San Francisco

Ophthalmology
David O. Harrington, San Francisco
Robert S. Hepler, Los Angeles

Orthopedics
Rodney K. Beals, Portland
John A. Blosser, Oakland
Paul E. McMaster, Beverly Hills

Otolaryngology
Mansfield F. W. Smith, San Jose
Paul H. Ward, Los Angeles

Pathology
Richard L. Kempson, Stanford
Averill A. Liebow, San Diego

Pediatrics
Robert E. Greenberg, Los Angeles
William L. Nyhan, San Diego
Henry R. Shinefield, San Francisco
Paul F. Wehrle, Los Angeles

Pharmacology
Sydney M. Finegold, Los Angeles
Kenneth L. Melmon, San Francisco

Physical Medicine and Rehabilitation
Elizabeth S. Austin, Los Angeles
Glenn G. Reynolds, San Jose

Plastic Surgery
Richard L. Dakin, San Rafael
N. John Wilde, Fresno

Psychiatry
Carl Eisdorfer, Seattle
Leon J. Epstein, San Francisco
George L. Mallory, Los Angeles
Helen Tausend, Los Angeles

Public Health
J. M. Stubblebine, Sacramento
Irma M. West, Sacramento

Radiology
H. Joachim Burhenne, San Francisco
Robert B. Engle, Pasadena
Melvin M. Figley, Seattle

Thoracic and Cardiac Surgery
John E. Connolly, Irvine
Albert Starr, Portland

Urology
Thomas F. Conroy, San Mateo
Ruben F. Gittes, La Jolla

Consultants in Medical Services and Health Care
Gerald A. Besson, Sunnyvale
Paul Scholten, San Francisco

Policy Committee—Editorial Board

STANLEY A. MOORE ..... San Diego
CARL GOETSCH ..... Berkeley
JOSEPH F. BOYLE ..... Los Angeles
HENRY V. EASTMAN ..... Tustin
E. KASH ROSE ..... Napa
ALBERT G. CLARK ..... San Francisco
MALCOLM S. M. WATTS ..... San Francisco

Advertisements—THE WESTERN JOURNAL OF MEDICINE is published the first week of each month. Advertising copy must be received not later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Advertising Committee.

SALES REPRESENTATIVES: JOHN H. HARLING, INC.

EAST:
SAUL HORNIK
655 AMBOY AVENUE
WOODBRIDGE, N.J. 07095
TEL. (201) 636-7150

MIDWEST:
JOHN HARLING • JAMES ANTON
18 SO. MICHIGAN AVE.
CHICAGO, ILL. 60603
TEL. (312) 641-0755

WEST:
MELVIN B. TYLER
731 MARKET ST.
SAN FRANCISCO, CA. 94103
TEL. (415) 777-2000

Copyright, 1974, by the California Medical Association.

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the non-commercial purpose of scientific or educational advancement.

Subscription prices, $8 ($9 for foreign countries); student subscription $4; single copies 80 cents.

Volumes begin with the first of January and the first of July. Subscriptions may commence at any time.

Change of Address—Requests for change of address should give both the old and new address.

CONTRIBUTIONS OF SCIENTIFIC AND ORIGINAL ARTICLES

Responsibilities for Statements and Conclusions in Original Articles—Authors are responsible for all statements, conclusions and methods of presenting their subjects. These may or may not be in harmony with the views of the editorial staff. It is aimed to permit authors to have as wide latitude as the general policy of the Journal and the demands on its space may permit. The right to reduce, revise or reject any manuscript is always reserved.

Exclusive Publication—Articles are accepted for publication on condition that they are contributed solely to this Journal. Ordinarily contributors will be notified within 60 days if a manuscript is accepted for publication. Every effort will be made to return unused manuscripts.

Length of Articles—Ordinarily articles should not exceed 3,000 words (approximately 5 printed pages). Under exceptional circumstances only will articles of over 4,000 words be published.

Manuscripts—Manuscripts should be typewritten, double spaced and the original typescript plus one copy submitted.

Illustrations—Ordinarily publication of 2 or 3 illustrations accompanying an article will be paid for by THE WESTERN JOURNAL OF MEDICINE. Any number beyond this might have to be paid for by the author.

References—Should conform to the following order: name of author, title of article, name of periodical, with volume, inclusive pages, month and year—i.e.: Lee GS: The heart rhythm following therapy with digitalis—In theory and practice. Arch Int Med 44:554-562, Dec 1942. They should be listed in the order in which they are cited in the text, numbered in sequence and punctuated as above.

Reprints—Reprints must be paid for by the author at established standard rates.

CONTRIBUTIONS OF "LETTERS TO THE EDITOR"

The Editorial Board will be glad to receive and consider for publication letters containing information of general interest to physicians or presenting constructive criticisms on issues of the day.

"Entered as second class matter at the post office in San Francisco and additional mailing offices under the Act of March 3, 1879." Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized August 10, 1918.

Free: "A Brief Guide to Tax-Exempt Municipal Bonds."

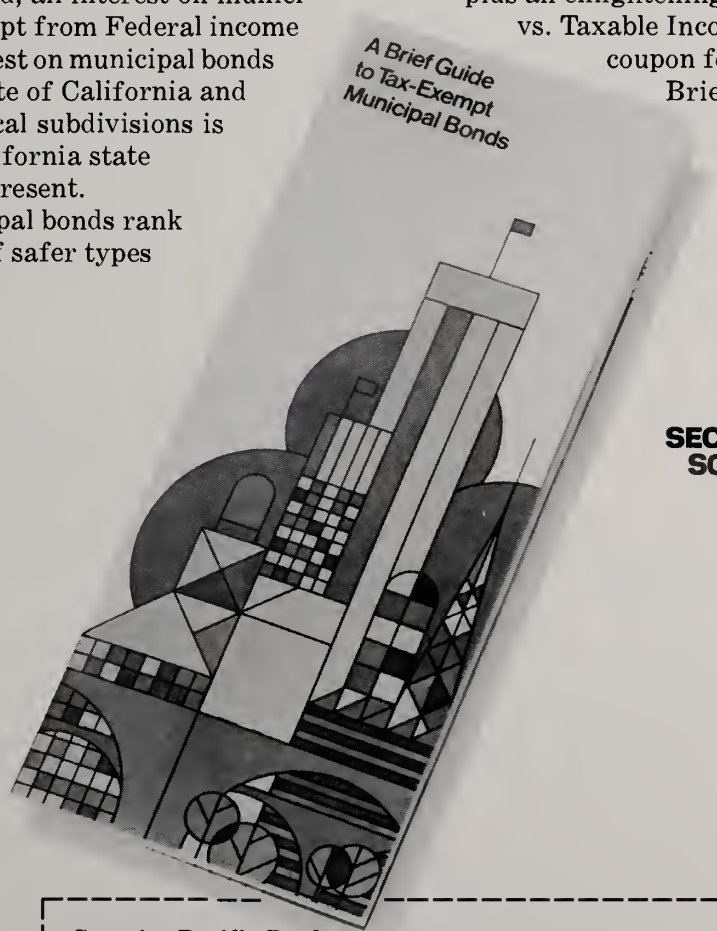
We'd like to send you a little booklet that covers several reasons for considering municipal bonds. Here are just two of them.

Simply stated, all interest on municipal bonds is exempt from Federal income taxes. Also, interest on municipal bonds issued by the State of California and most of its political subdivisions is exempt from California state income taxes at present.

And, municipal bonds rank high on the list of safer types of investment.

These are only two of several sound reasons you should consider municipal bonds as an investment vehicle. For more reasons, plus an enlightening chart of Tax-Exempt vs. Taxable Income, please return the coupon for our free booklet, "A Brief Guide to Tax-Exempt Municipal Bonds."

There is, of course, no obligation.



SECURITY PACIFIC BANK
SOMETHING SPECIAL

Security Pacific Bank
Municipal Bond Department
P. O. Box 2097
Terminal Annex
Los Angeles, California 90054

Name _____

Address _____

City _____

State _____ Zip Code _____

EMBER FDIC

© 1974 SPNB

Part of a series on the clinical, bacteriological and pharmacological aspects of Bactrim therapy.

This is Bactrim against E. coli, Proteus

These are results from clinical trials* in which patients with chronic urinary tract infections (primarily cystitis, pyelitis and pyelonephritis), more than half with obstructive complications, were treated with Bactrim for 10 days and evaluated at intervals up to 32 days after termination of therapy. Patients were considered to have a significant bacteriological response when the urine culture revealed 10,000 or fewer colonies/ml of any single organism cultured from a midstream clean-catch specimen.

Before prescribing Bactrim, please consult complete product information for all adverse reactions, contraindications, precautions and warnings.

ROCHE

performance
spp. and Klebsiella

	Excellent initial response* after 10 days of therapy	Impressive response maintained 32 days after termination of therapy
E. coli infections	97.1% of 105 patients	73.1% of 93 patients
Proteus spp. infections	81.1% of 37 patients	60.0% of 35 patients
Klebsiella infections	85.7% of 21 patients	65.0% of 20 patients

ata on file, Medical Department, Hoffmann-La Roche Inc., Nutley, New Jersey

Bactrim™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

In cystitis, pyelonephritis and pyelitis diagnosed as chronic and due to susceptible urinary tract pathogens, usually E. coli, Klebsiella-Enterobacter and Proteus mirabilis.

Please see following page for summary of product information.

In cases of cystitis, pyelonephritis and pyelitis diagnosed as chronic*

Bactrim™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

- aggressive antibacterial activity
- interrupts essential metabolic process of susceptible organisms, usually E. coli, Klebsiella-Enterobacter, P. mirabilis, and, less frequently, indole-positive proteus species
- over 91% initial efficacy in clinical studies of patients with urinary tract infection diagnosed as chronic*
- impressive response even in cases with obstructive complications
- not recommended for children under 12, during pregnancy or the nursing period
- no loading dose; two tablets b.i.d. recommended for 10-14 days

*due to susceptible organisms

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Enterobacter, Proteus mirabilis,* and, less frequently, indole-positive proteus species).

NOTE: The increasing frequency of resistant organisms limits the usefulness of antibacterials, especially in chronic and recurrent urinary tract infections.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia in elderly patients on diuretics, primarily thiazides. Sore throat, fever, pallor or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted. Data are insufficient to recommend use in infants and children under 12.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, allergy or bronchial asthma; and in those with glucose-6-phosphate dehydrogenase deficiency, where hemolysis may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for children under 12. Usual adult dosage: Two tablets b.i.d. for 10 to 14 days. For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	2 tablets every 24 hours
Below 15	Use not recommended

Supplied: Tablets, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40, available singly and in trays of 10.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Good news for saturated fat watchers...

New Matey® Sour Dressing. Low in saturated fat, Cholesterol free!

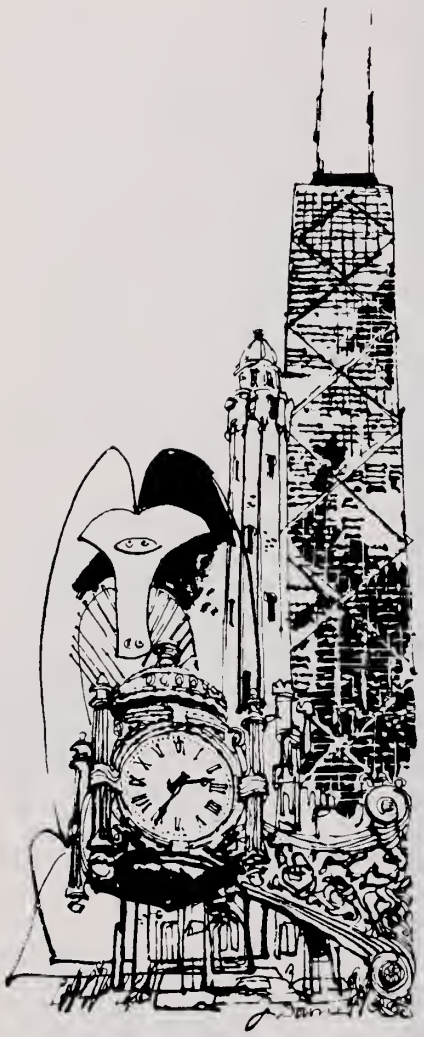
Imagine. A sour dressing you can feel free to recommend. One that gives all the satisfaction of the one you had to restrict, but that has a relative saturated fat to total fat of only 18% as compared to over 50% for dairy sour cream. What's more, delicious new Matey® Non-Dairy Lo Saturate Sour Dressing is made from a blend of liquid safflower and soybean oils (the only one that is) and is *completely cholesterol free.*

If your patients are bored with a saturated fat restricted diet, they'll love the way new Matey can liven up their menu. Great for dips, on baked potatoes, fruit salad or cooking ...anywhere a sour dressing is called for.

New Matey. You'll find it in your grocer's dairy case now. Better yet, write for a free supply of coupons so you and your patients can sample it free. We'll also send you a complete data sheet for your files.

Presto Food Products, Inc.
Box 21908,
Los Angeles,
Calif. 90021

Made by the makers of Mocha Mix®...the non-dairy creamer that's lowest in saturated fat. Both available in larger sizes for hospitals and institutions.



123rd

AMA ANNUAL CONVENTION
JUNE 22-26, 1974
CHICAGO, McCORMICK PLACE

- *Scientific Sessions* including Hypertension/Management of Obesity/A Practitioner's Approach to Angina—1974
- *Postgraduate Courses* including Cardiopulmonary Resuscitation/Total Parenteral Nutrition/Workshop on Human Sexuality/American Society of Clinical Pathologists: special courses for non-pathologists
- *Fireside Forums*—return of a popular evening session in a new "meet the professor" format
- *Scientific Exhibits* including Clinical Pathologic Conferences/Live Teaching Clinic/Fresh Tissue Pathology
- *Film Symposia* including a ½-day session on techniques of producing a medical motion picture in your hospital
- *Charter flights* are being planned from Los Angeles, San Francisco and Dallas.

Write a letter with the coupon below to the AMA or see the JAMA Convention Issue on April 15, 1974, for scientific session lists, hotel reservations, and course registrations—as well as social activities while in Chicago this June.

Advance Registration

123rd AMA Annual Convention
June 22-26, 1974
Chicago/McCormick Place

Please return this form before May 24, 1974, to:
Circulation and Records Department
American Medical Association
535 North Dearborn Street
Chicago, Illinois 60610

Please print

Name _____
(each physician must register in his own name)

Office Address _____

City/State/Zip _____

I am a member of the AMA through the following State Medical Association or government service _____

Please send more information on the charter flights being planned from:

___Los Angeles ___San Francisco ___Dallas

In accordance with the AMA Bylaws, I hold active membership in the AMA, and I wish to vote in the Scientific Session I have checked:

01 ☐ Allergy
02 ☐ Anesthesiology
26 ☐ Cardiovascular Diseases
05 ☐ Clinical Pharmacology and Therapeutics
20 ☐ Colon and Rectal Surgery
03 ☐ Dermatology
04 ☐ Diseases of the Chest
07 ☐ Family and General Practice
11 ☐ Federal and Military Medicine
06 ☐ Gastroenterology
08 ☐ General Surgery
09 ☐ Internal Medicine
24 ☐ Neurological Surgery
25 ☐ Neurology
13 ☐ Obstetrics and Gynecology
14 ☐ Ophthalmology
15 ☐ Orthopedic Surgery
10 ☐ Otorhinolaryngology
16 ☐ Pathology
17 ☐ Pediatrics
18 ☐ Physical Medicine and Rehabilitation
27 ☐ Plastic and Reconstructive Surgery
19 ☐ Preventive Medicine
12 ☐ Psychiatry
21 ☐ Radiology
22 ☐ Urology

General Registration
___AMA members and their guests: no fee
___Non-member physicians: $25
___Guests of non-members: $5
___Medical students, interns and residents: no fee

My remittance of $_____ is enclosed.
(Make check payable to American Medical Association.)
Check must accompany registration.

first came the
ANTIHISTAMINES
and the
PHENOTHIAZINES

and now...

a NEW effective antinausean for use in anest

Chemically unique

Emete-con (benzquinamide HCl) is chemically unrelated to the phenothiazines and to other anti-emetics. It is a non-amine-depleting benzoquinolizine derivative.

Effective

Efficacy comparable to a standard phenothiazine, demonstrated in well-control clinical studies.*

on-phenothiazine antiemetic sia and surgery

Well tolerated
Drowsiness appears to be the most common reaction. Other more significant reactions have been reported; please refer to the package insert.

New Emete-con™ (benzquinamide HCl) IM/IV

Usual adult dose: IM-50 mg., IV-25 mg.

For prescribing information, including adverse reactions and [illegible] please see full prescribing [illegible]

Roerig introduces NEW

Emete-con™

(benzquinamide HCl)IM/IV

PRESCRIBING INFORMATION
Emete-con™ (Benzquinamide-Hydrochloride)
For Intramuscular and Intravenous Use

Description. Benzquinamide is a non-amine-depleting benzoquinolizine derivative, chemically unrelated to the phenothiazines and to other antiemetics.

Chemically, Emete-con (benzquinamide-hydrochloride) is N, N-diethyl-1,3,4,6,7,11b-hexahydro-2-hydroxy-9, 10-dimethoxy-2H-benzo(a)quinolizine-3-carboxamide acetate hydrochloride. The empirical formula is $C_{22}H_{32}N_2O_5$. HCl and the molecular weight is 441.

Emete-con for injection contains: Benzquinamide HCl equivalent to benzquinamide 50 mg/vial and citric acid 1%. When reconstituted with 2.2 ml of sterile water for injection, each vial yields 2 ml of a solution containing benzquinamide, 25 mg/ml. When reconstituted, this product maintains its potency for 14 days at room temperature. DO NOT REFRIGERATE.

Actions. Benzquinamide HCl exhibited antiemetic, antihistaminic, mild anticholinergic and sedative action in animals. Studies conducted in dogs and human volunteers have demonstrated suppression of apomorphine-induced vomiting; however, relevance to clinical efficacy has not been established. The mechanism of action in humans is unknown. The onset of antiemetic activity in humans usually occurs within 15 minutes.

Benzquinamide metabolism has been studied in animals and in man. In both species, 5-10% of an administered dose is excreted unchanged in the urine. The remaining drug undergoes metabolic transformation in the liver by at least three pathways to a spectrum of metabolites which are excreted in the urine and in the bile, from which the more polar metabolites are not reabsorbed but are excreted in the feces. The half-life in plasma of Emete-con is about 40 minutes. More than 95% of an administered dose was excreted within 72 hours in animal studies using C14-labeled benzquinamide. In blood, benzquinamide is about 58% bound to plasma protein.

Indications. Emete-con is indicated for the prevention and treatment of nausea and vomiting associated with anesthesia and surgery.

Since the incidence of postoperative and postanesthetic vomiting has decreased with the adoption of modern techniques and agents, the prophylactic use of Emete-con should be restricted to those patients in whom emesis would endanger the results of surgery or result in harm to the patient.

Contraindications. Emete-con is contraindicated in individuals who have demonstrated hypersensitivity to the drug.

Warnings. *Use in Pregnancy:* No teratogenic effects of benzquinamide were demonstrated in reproduction studies in chick embryos, mice, rats and rabbits. The relevance of these data to the human is not known. However, safe use of this drug in pregnancy has not been established and its use in pregnancy is not recommended.

Use in Children: As the data available at present are insufficient to establish proper dosage in children, the use of Emete-con in children is not recommended.

Intravenous use: Sudden increase in blood pressure and transient arrhythmias (premature ventricular and auricular contractions) have been reported following intravenous administration of benzquinamide. Until a more predictable pattern of the effect of intravenous benzquinamide has been established, the intramuscular route of administration is considered preferable. The intravenous route of administration should be restricted to patients without cardiovascular disease and receiving no pre-anesthetic and/or concomitant cardiovascular drugs.

Precautions. Benzquinamide, like other antiemetics, may mask signs of overdosage of toxic drugs or may obscure diagnosis of such conditions as intestinal obstruction and brain tumor.

Adverse Reactions. The following adverse reactions have been reported in subjects who have received benzquinamide. Because of the multiplicity of medications commonly used in the practice of anesthesia, unequivocal relationship to a specific drug administered usually cannot be established. However, drowsiness appears to be the most common reaction. One case of pronounced allergic reaction has been encountered, characterized by pyrexia and urticaria.

System Affected—*Autonomic Nervous System:* Dry mouth, shivering, sweating, hiccoughs, flushing, salivation, blurred vision.

Cardiovascular System: Hypertension, hypotension, dizziness, atrial fibrillation, premature auricular and ventricular contractions.

Central Nervous System: Drowsiness, insomnia, restlessness, headache, excitement, nervousness.

Gastrointestinal System: Anorexia, nausea.

Musculoskeletal System: Twitching, shaking/tremors, weakness.

Skin: Hives/rash.

Other Systems: Fatigue, chills, increased temperature.

Dosage and Administration. *Intramuscular:* 50 mg (0.5 mg/kg–1.0 mg/kg)

First dose may be repeated in one hour with subsequent doses every 3-4 hours, as necessary. The precautions applicable to all intramuscular injections should be observed. Emete-con should be injected well within the mass of a larger muscle. The deltoid area should be used only if well developed. Injections should not be made into the lower and mid-thirds of the upper arm. Aspiration of the syringe should be carried out to avoid inadvertent intravascular injection.

Therapeutic blood levels and demonstrable antiemetic activity appear within fifteen minutes of intramuscular administration. When the objective of therapy is the prevention of nausea and vomiting, intramuscular administration is recommended at least fifteen minutes prior to emergence from anesthesia.

Intravenous: 25 mg (0.2 mg/kg–0.4 mg/kg as a single dose) administered slowly (1 ml per 0.5 to 1 minute). Subsequent doses should be given intramuscularly.

The intravenous route of administration should be restricted to patients without cardiovascular disease (See WARNINGS). If it is necessary to use Emete-con intravenously in elderly or debilitated patients, benzquinamide should be administered cautiously and the lower dose range is recommended.

This preparation must be initially reconstituted with 2.2 ml of sterile water. This procedure yields 2 ml of a solution equivalent to 25 mg benzquinamide/ml, which maintains its potency for 14 days at room temperature.
DO NOT REFRIGERATE.

Overdosage. *Manifestations:* On the basis of acute animal toxicology studies, gross Emete-con overdosage in humans might be expected to manifest itself as a combination of Central Nervous System stimulant and depressant effects. This speculation is derived from experimental studies in which intravenous doses of benzquinamide, at least 150 times the human therapeutic dose, were administered to dogs.

Treatment: There is no specific antidote for Emete-con overdosage. General supportive measures should be instituted, as indicated. Atropine may be helpful. Although there has been no direct experience with dialysis, it is not likely to be of value, since benzquinamide is extensively bound to plasma protein.

How Supplied. Emete-con for IM/IV use is available in a vial containing benzquinamide HCl equivalent to 50 mg of benzquinamide in packages of 10 vials.

Caution. Federal law prohibits dispensing without prescription.

Bibliography

Zauder, H.L., et al.: Prophylaxis of Postoperative Emesis, Scientific Exhibit presented at 122nd Annual Convention of the A.M.A., June 23-27, 1973.

Lutz, H., and Immich, H.: Antiemetic effect of benzquinamide in postoperative vomiting. Curr. Ther. Res. 14:178, April, 1972.

Finn, H., et al.: Antiemetic efficacy of benzquinamide. N.Y. J. Med. 71:61, March 15, 1971.

Larrauri, R.M.: Benzquinamide parenteral for the treatment of post-operative nausea and vomiting. Curr. Ther. Res. 11:65, March, 1969.

ROERIG Pfizer

A division of Pfizer Pharmaceuticals
New York, New York 10017

New Emete-con™

(benzquinamide HCl)IM/IV

Each vial contains benzquinamide hydrochloride equivalent to 50 mg. of benzquinamide with 0.45 mg. of citric acid.

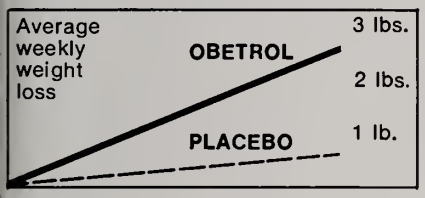
EFFECTIVE APPETITE DEPRESSANT with predictable pharmacological action

OBETROL® CII

Single entity amphetamine product. Each OBETROL-10 (10 mg. tablet) contains: dextroamphetamine saccharate 2.5 mg., amphetamine aspartate 2.5 mg., dextroamphetamine sulfate 2.5 mg., amphetamine sulfate 2.5 mg. OBETROL-20 (20 mg. tablets) contain twice this potency.

Average weight loss of 2.15 lbs per week compared in clinical studies against a placebo.

CONTROLLED STUDY —
72 CASES 4 WEEKS' RESULTS



Obetrol eases the discomfort of adherence to a restricted diet in individuals who are well motivated to reduce their food intake.

Clinical studies disclose amphetamines to be the most dependable drug in a weight-reduction regimen compared to other anorexigenic agents.

Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.
Indications: Erogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.
Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.
Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.
Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.
Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.
Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.
1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
   a. Not recommended for children under 3 years of age.
   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, once or twice daily, increased in increments of 5 milligrams at weekly intervals. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.
Availability: Supplied in bottles of 100; 500 and 1,000 tablets.
CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.
January 1973

Comprehensive informational brochure available upon written request. Prescribe Obetrol for appetite control.

OBETROL Pharmaceuticals Division/Rexar Pharmacal Corp.
Valley Stream, New York 11582

Must vasodilators and therapy for other diseases come into conflict?

not if the vasodilator is

VASODILAN®

(ISOXSUPRINE HCl)

the compatible vasodilator... no treatment conflicts reported

The cerebral or peripheral vascular disease patient often has coexisting disease[1] which calls for another drug along with his vasodilator. It may be a hypoglycemic, miotic, antihypertensive, diuretic, anticoagulant, corticosteroid, or coronary vasodilator.

Vasodilan is not incompatible with any of these drugs—no treatment conflict has been reported. And, unlike other vasodilators, Vasodilan has not been reported to affect carbohydrate metabolism, liver function, or intraocular pressure—or to complicate treatment of diabetes, hypertension, peptic ulcer, glaucoma, or liver disease.

In fact, there are no known contraindications to the use of Vasodilan in recommended oral doses, other than that it should not be given in the presence of frank arterial bleeding or immediately postpartum.

1. Gertler, M. M., et al.: Geriatrics *25*:134-148 (May) 1970.

Indications: Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.
3. Threatened abortion.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.

Dosage and Administration: 10 to 20 mg. three or four times daily.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Adverse Reactions: On rare occasions, oral administration of the drug has been associated in time with the occurrence of severe rash. When rash appears, the drug should be discontinued. Occasional overdosage effects such as transient palpitation or dizziness are usually controlled by reducing the dose.

Supplied: Tablets, 10 mg.—bottles of 100, 1000, 5000 and Unit Dose; 20 mg.—bottles of 100, 500 and Unit Dose.

© 1973 MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA 47721, U.S.A. 734017

Mead Johnson LABORATORIES

Case history #6

Vernon's well-being comes first.

Vernon's being well comes first.

On October 26, 1963, Vernon Bailey was working atop an oil derrick in Bakersfield 'hen he lost his footing and fell 35 feet to the ground, suffering a spinal injury with per-ıanent paraplegia. The hardest years of his life began.

State Compensation Insurance Fund helped the primary physician to transfer Vernon nmediately to a Spinal Cord Center, where he was taught the necessary medical tech-iques and skills of self-care that would enable him to live as full and normal a life as ɔssible.

For the next ten years, State Fund's rehabilitation team worked closely with Vernon ıd his doctors in helping to rebuild his life.

Today, although Vernon has been unable to return to work, his financial future is ɜcure. Arrangements were made for Vernon to receive a lump-sum payment of his projected fetime benefits, and State Fund helped him invest the money wisely.

Vernon has come a long way since 1963. His problems aren't over, but he has built imself a future—with the help of State Fund.

Conserving your human resources is our only business

STATE COMPENSATION INSURANCE FUND

What's on your patient's face...

may be more important than his chief complaint

Patient P.T.* seen on 3/29/67 shows typical lesions of moderately severe keratoses. Note residual scarring on ridge of nose from previous cryosurgical and electrosurgical procedures.

Patient P.T.* seen on 6/12/67, seven weeks after discontinuation of 5% FU cream. Reaction has subsided. Residual scarring not seen except that due to prior surgery. Inflammation has cleared and face is clear of keratotic lesions.

*Data on file, Hoffmann-La Roche Inc., Nutley, N.J

The lesions on his face are solar/actinic— so-called "senile" keratoses... and they may be premalignant.

Solar, actinic or senile keratoses

These lesions may be called by several names, but they usually can be identified by the following characteristics. The typical lesion is flat or slightly elevated, of a brownish or reddish color, papular, dry, rough, adherent and sharply defined. They commonly occur as multiple lesions, chiefly on the exposed portions of the skin.

Sequence of therapy— selectivity of response

After several days of therapy with Efudex® (fluorouracil), erythema may begin to appear in the area of the lesions; this reaction usually reaches its height of unsightliness and discomfort within two weeks, declining after discontinuation of therapy. This reaction occurs in affected areas. Since the response is so predictable, lesions that do not respond should be biopsied.

Acceptable results

Treatment with Efudex provides highly favorable cosmetic results. Incidence of scarring is low. This is particularly important with multiple facial lesions. Efudex should be applied with care near the eyes, nose and mouth.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Multiple actinic or solar keratoses.

Contraindications: Patients with known hypersensitivity to any of its components.

Warnings: If occlusive dressing used, may increase inflammatory reactions in adjacent normal skin. Avoid prolonged exposure to ultraviolet rays. Safe use in pregnancy not established.

Precautions: If applied with fingers, wash hands immediately. Apply with care near eyes, nose and mouth. Lesions failing to respond or recurring should be biopsied.

Adverse Reactions: Local—pain, pruritus, hyperpigmentation and burning at application site most frequent; also dermatitis, scarring, soreness and tenderness. Also reported—insomnia, stomatitis, suppuration, scaling, swelling, irritability, medicinal taste, photosensitivity, lacrimation, leukocytosis, thrombocytopenia, toxic granulation and eosinophilia.

Dosage and Administration: Apply sufficient quantity to cover lesion twice daily with nonmetal applicator or suitable glove. Usual duration of therapy is 2 to 4 weeks.

How Supplied: Solution, 10-ml drop dispensers—containing 2% or 5% fluorouracil on a weight/weight basis, compounded with propylene glycol, tris(hydroxymethyl)-aminomethane, hydroxypropyl cellulose, parabens (methyl and propyl) and disodium edetate.

Cream, 25-Gm tubes—containing 5% fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60 and parabens (methyl and propyl).

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

This patient's lesions were resolved with

Efudex®

fluorouracil/Roche®

5% cream/solution...a Roche exclusive

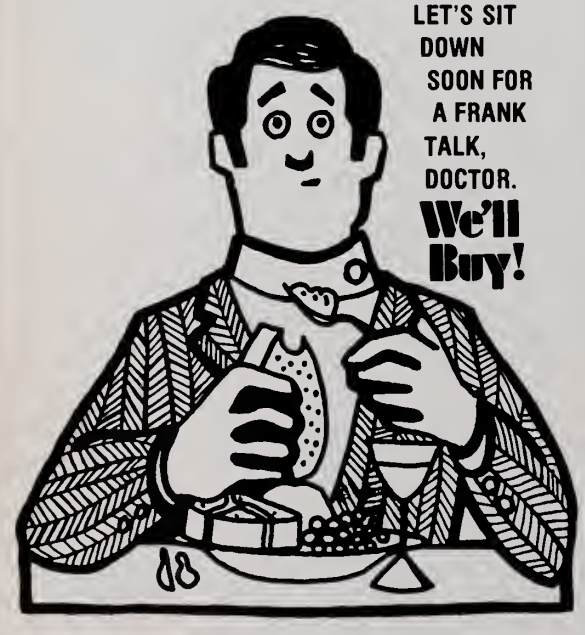
When was the last time you made money at lunch, Doctor?

Right off we'll assure you of at least a break even—*we'll buy lunch!*

Beyond that, our service to nearly 2,000 doctors should qualify us as an organization with an understanding and appreciation of the problems of the professional man.

Simply, and there is much more to it, we are a unique firm, organized to provide the health care professions with the means to free-up capital and then prudently invest to produce additional wealth.

But we can't recommend until we know you and you know us. We feel that we have a program to meet every need—but first we must work with you to isolate that need.



medi-fund

The Medi-Fund Corporation
525 SPRUCE ST.
San Francisco, Ca. 94118

Please tell me more about these services

- ☐ Profit center lease
- ☐ New equipment lease
- ☐ New practice lease
- ☐ New equipment rental
- ☐ Tax shelter investments
- ☐ Purchase leaseback

Name _____

Address _____

City _____ State _____ Zip _____

PROLOID® (thyroglobulin)

Caution: Federal law prohibits dispensing without prescription.

Description. Proloid (thyroglobulin) is obtained from a purified extract of frozen hog thyroid. It contains the known calorigenically active components, Sodium Levothyroxine (T_4) and Sodium Liothyronine (T_3). Proloid (thyroglobulin) conforms to the primary USP specifications for desiccated thyroid—for iodine based or chemical assay—and is also biologically assayed and standardized in animals.

Chromatographic analysis to standardize the Sodium Levothyroxine and Sodium Liothyronine content of Proloid (thyroglobulin) is routinely employed.

The ratio of T_4 and T_3 in Proloid (thyroglobulin is approximately 2.5 to 1.

Proloid (thyroglobulin) is stable when stored at usual room temperature.

Indications. Proloid (thyroglobulin) is thyroid replacement therapy for conditions of inadequate endogenous thyroid production: e.g. cretinism and myxedema. Replacement therapy will be effective only in manifestations of hypothyroidism.

In simple (nontoxic) goiter, Proloid (thyroglobulin) may be tried therapeutically, in non emergency situations, in an attempt to reduce the size of such goiters.

Contraindication. Thyroid preparations are contraindicated in the presence of uncorrected adrenal insufficiency.

Warnings. Thyroglobulin should not be used in the presence of cardiovascular disease unless thyroid-replacement therapy is clearly indicated. If the latter exists, low doses should be instituted beginning at 0.5 to 1.0 grain (3 to 64 mg) and increased by the same amount in increments at two-week intervals. This demands careful clinical judgment.

Morphologic hypogonadism and nephrosis should be ruled out before the drug is administered. If hypopituitarism is present, the adrenal deficiency must be corrected prior to starting the drug.

Myxedematous patients are very sensitive to thyroid and dosage should be started at a very low level and increased gradually.

Precaution. As with all thyroid preparations this drug will alter results of thyroid function tests.

Adverse Reactions. Overdosage or too rapid increase in dosage may result in signs and symptoms of hyperthyroidism, such as menstrual irregularities, nervousness, cardiac arrhythmias, and angina pectoris.

Dosage and Administration. Optimal dosage is usually determined by the patient's clinical response. Confirmatory tests include BMR, T_4 ^{131}I resin sponge uptake, T_3 ^{131}I red cell uptake, Thyro Binding Index (TBI), and Achilles Tendon Reflex Test. Clinical experience has shown that a normal PBI (3.5-8 mcg/100 ml) will be obtained in patients made clinically euthyroid when the content of T_4 and T_3 is adequate. Dosage should be started in small amounts and increased gradually with increments at intervals of one to two weeks. Usual maintenance dose is 0.5 to 3.0 grains (32 to 190 mg) daily.

Overdosage Symptoms. Headache, instability, nervousness, sweating, tachycardia, with unusual bowel motility. Angina pectoris or congestive heart failure may be induced or aggravated. Shock may develop. Massive overdosage may result in symptoms resembling thyroid storm. Chronic excessive dosage will produce the signs and symptoms of hyperthyroidism.

(Treatment: In shock, supportive measures should be utilized. Treatment of unrecognized adrenal insufficiency should be considered.)

How Supplied. ¼ grain; ½ grain; scored grain; 1½ grain; scored 2 grain; 3 grain; and scored 5 grain tablets, in bottles of 100 and 1000.

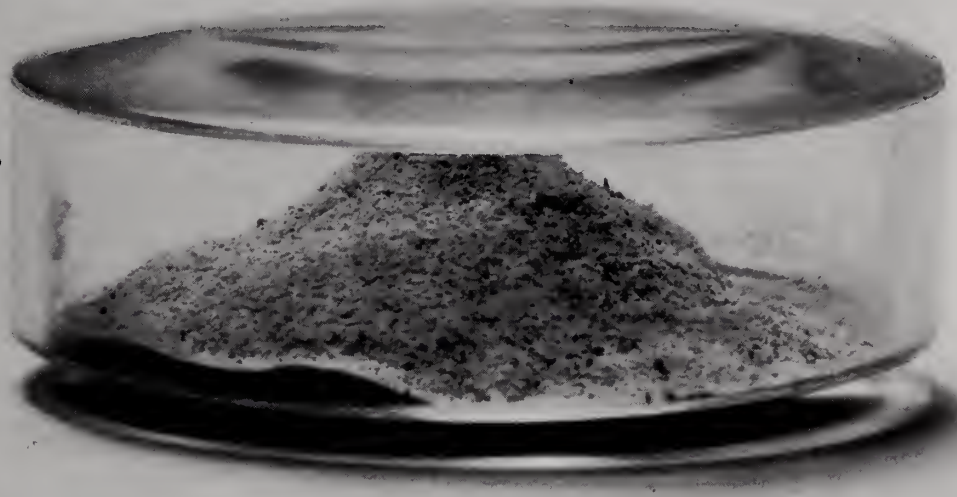
Full information available on request.

WC **WARNER/CHILCOTT**
Division, Warner-Lambert Company
Morris Plains, New Jersey 07950

PR-CP-31-B/W

IN NATURAL THYROID THERAPY:

ARE PATIENTS GETTING THE POTENCY YOU PRESCRIBE?



Unlike U.S.P. desiccated thyroid, Proloid® (thyroglobulin) offers the assurance of constant potency.

To begin with, Proloid is uniquely purified. The thyroglobulin extracted from hog thyroid is devoid of any glandular debris.

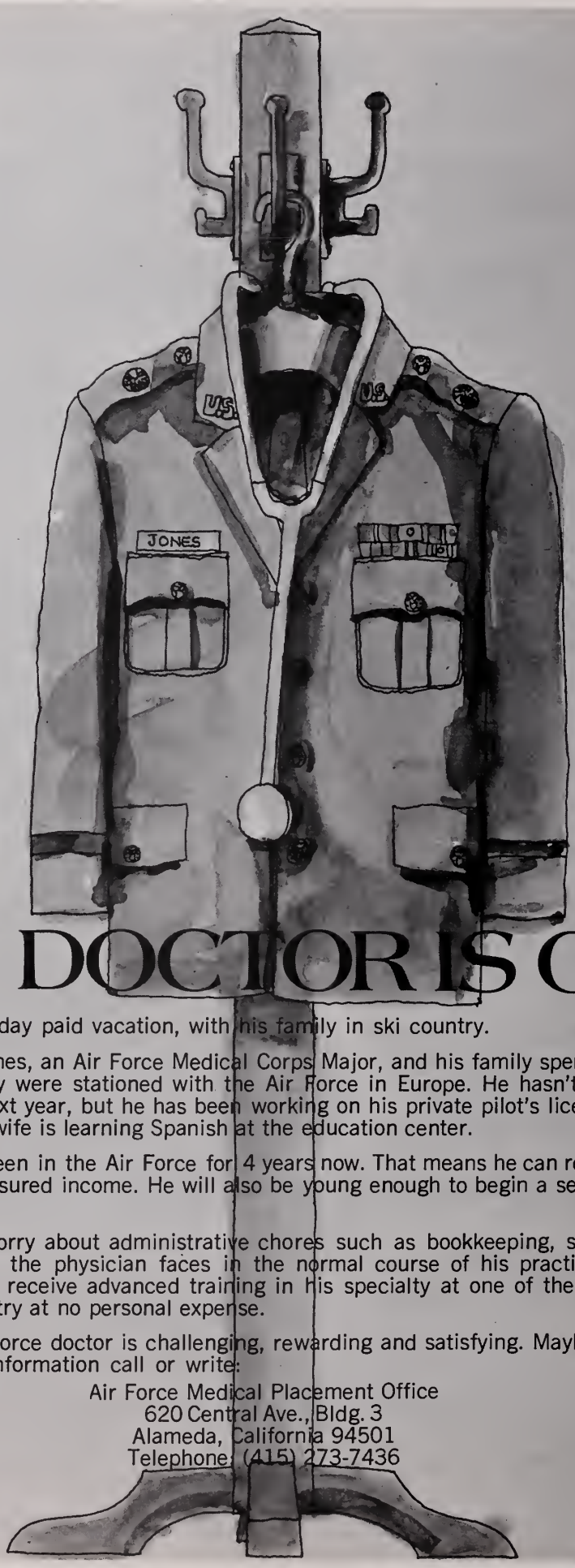
Then, Proloid is chemically and biologically assayed to assure consistent metabolic activity from batch to batch. The T_4 and T_3 content of every dose is blended for optimal thyroid replacement.

Important, too, is the fact that Proloid is invariably "fresh" when your patients take it. Under proper storage conditions, its potency will not diminish for at least four years.

All of which adds up to this: the potency of Proloid is constant...for more consistent results.

PROLOID®
(thyroglobulin)

natural thyroid therapy that leaves nothing to chance



THE DOCTOR IS OUT

He's enjoying a 30 day paid vacation, with his family in ski country.

Last year Doctor Jones, an Air Force Medical Corps Major, and his family spent their vacation in Switzerland. They were stationed with the Air Force in Europe. He hasn't said what they have planned for next year, but he has been working on his private pilot's license at the base flying club and his wife is learning Spanish at the education center.

Doctor Jones has been in the Air Force for 4 years now. That means he can retire in less than 16 years with an assured income. He will also be young enough to begin a second successful career.

He won't have to worry about administrative chores such as bookkeeping, supplies, rent or the other problems the physician faces in the normal course of his practice. And he was recently selected to receive advanced training in his specialty at one of the finest research centers in the country at no personal expense.

The life of the Air Force doctor is challenging, rewarding and satisfying. Maybe it's your kind of life? For more information call or write:

Air Force Medical Placement Office
620 Central Ave., Bldg. 3
Alameda, California 94501
Telephone: (415) 273-7436

When the asthmatic can anticipate the attack Bronkotabs®

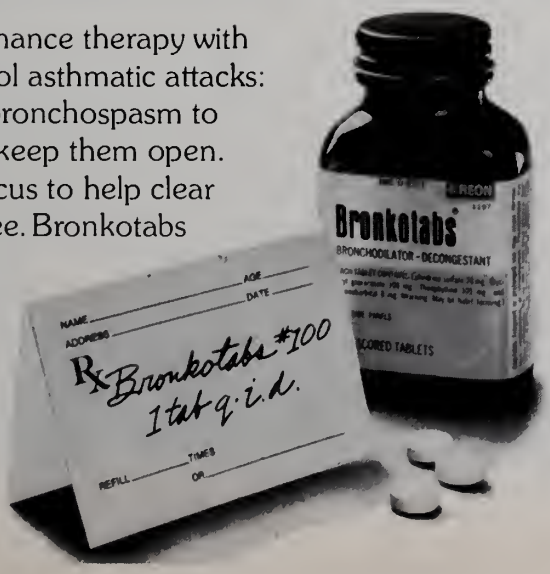
Each tablet contains ephedrine sulfate 24 mg; theophylline 100 mg; glyceryl guaiacolate 100 mg; phenobarbital 8 mg (warning: may be habit-forming).

can help forestall or relieve it

Why day to day maintenance therapy with Bronkotabs helps control asthmatic attacks:

Bronkotabs relieves bronchospasm to open airways and help keep them open.

Bronkotabs thins mucus to help clear the tracheobronchial tree. Bronkotabs decongests bronchiolar mucosa to improve the passage of air. Economical long-term therapy.



PRECAUTIONS AND ADVERSE EFFECTS: Sympathomimetic side effects are minimal, and there are none of the dangers or side effects associated with steroid therapy. However, frequent or prolonged use may cause nervousness, restlessness or sleeplessness. Should be used with caution in the presence of hypertension, heart disease or hyperthyroidism. Drowsiness may occur. Ephedrine may cause urinary retention, especially in the presence of partial obstruction, as in prostatism.

DOSAGE: Adults, one tablet every three or four hours, four or five times daily. Children over six, one-half the adult dose. Children under six, as directed.

SUPPLIED: Bottles of 100 and 1,000 tablets.

BREON

BREON LABORATORIES INC.
90 Park Avenue, New York, N.Y. 10016

Kefzol®

cefazolin sodium

Ampoules, equivalent to 1 Gm. of cefazolin

Lilly

Additional information available to the profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206
400380

THE WESTERN
Journal of Medicine

Refer to: Reynolds MD, Rankin TJ: Diagnosis of "rheumatoid variants"—Ankylosing spondylitis, the arthritides of gastrointestinal diseases and psoriasis, and Reiter's syndrome. West J Med 120:441-447, Jun 1974

Diagnosis of "Rheumatoid Variants"

Ankylosing Spondylitis, the Arthritides of Gastrointestinal Diseases and Psoriasis, and Reiter's Syndrome

MICHAEL D. REYNOLDS, MD, *and* THOMAS J. RANKIN, MD, *Orange, California*

Four rheumatic diseases—ankylosing spondylitis, the arthritis accompanying ulcerative colitis or regional enteritis, psoriatic arthropathy, and Reiter's syndrome—formerly considered to be forms of rheumatoid arthritis, are now distinguished from that disorder and should be recognized by the physician as entities. These arthritides may be distinguished from each other by a number of clinical and radiographic characteristics, principally (1) the roentgenographic appearance of the spine when spondylitis is present, (2) the location of periosteal new bone formation, (3) the location of arthritis in the joints of the limbs, and (4) the presence of characteristic skin lesions.

THE RHEUMATIC DISORDERS which can produce widespread spondylitis were formerly regarded as "variants" of rheumatoid arthritis. Because of significant clinical and pathogenetic differences between them and rheumatoid disease, they now are accorded status as separate entities.[1] However, the term *rheumatoid variants* retains some utility to denote a group of diseases with some striking similarities: ankylosing (formerly rheumatoid) spondylitis, the arthritis which sometimes accompanies ulcerative colitis or regional enteritis, arthritis with psoriasis, and Reiter's syndrome. Because these disorders are characterized by their ability to affect both the spine and the peripheral joints, they also have been called "spondyloarthropathies." In this paper we review similarities and differences of members of this group as they apply to diagnosis and differential diagnosis.

From the Division of Rheumatology, Department of Medicine, University of California, Irvine, California College of Medicine, Irvine.

Submitted, revised, January 31, 1974.

Reprint requests to: M. D. Reynolds, MD, Department of Medicine, Orange County Medical Center, 101 The City Drive South, Orange, CA 92668.

Spondylitis

Rheumatoid arthritis of adults, when it affects the spine, usually is confined to the cervical area; the lumbo-sacral spine is not often involved.[2] The spondylo-arthropathies are distinguished by their production in some victims of inflammatory disease of the spine which can involve the entire length of the vertebral column. The character of the spondylitis serves to divide these diseases into two subgroups, as described in a study in which one of us (T.R.) participated.[3] McEwen and his associates first called attention[4] to differences between ankylosing spondylitis and spondylitis with ulcerative colitis on one hand, and the spinal disease accompanying psoriasis and Reiter's syndrome, on the other. Spinal inflammation of anky-

Figure 1.—Roentgenogram of a segment of lumbar spine of a patient with ankylosing spondylitis, showing ossification of spinal ligaments at borders of anuli fibrosi. The syndesmophytes arise from the margins of the vertebral bodies.

Figure 2.—Roentgenogram of a segment of lumbar spine of a patient with psoriatic spondylitis, showing ossification of spinal ligaments distant from the anuli fibrosi. Syndesmophytes arise from the mid-portions of the vertebral bodies (non-marginal), and may be hook-shaped or comma-shaped.

losing spondylitis and gastrointestinal disease (either ulcerative colitis or Crohn's disease) is expressed by calcification of ligaments (syndesmophytosis) immediately adjacent to the intervertebral discs (Figure 1). But in 50 percent or more of cases of spondylitis associated with psoriasis and Reiter's disease, syndesmophytes form also in the outer layer of para-spinal ligaments (Figure 2), an observation first reported by Bunim.[5] Ankylosing spondylitis and that accompanying enteric disease can therefore be grouped in a category 1, while the spinal arthritides of psoriasis and Reiter's syndrome constitute a category 2. A close relationship between psoriasis and Reiter's syndrome has also been proposed on grounds of clinical and other radiologic similarities.[6]

Ankylosing spondylitis is a prototype of subgroup 1. Several reviews of this disease have recently been published.[7-9] It is predominantly a disorder of young men, usually beginning with back pain and stiffness. Systemic symptoms—fever and weight loss—may be present. Bilateral sacro-iliitis occurs in almost every case;[10] inflammation usually follows an ascending pattern and may eventually extend to the cervical spine. Involvement of costochondral and manubrio-sternal joints often is present but overlooked. This disorder can and should be diagnosed long before the characteristic flexion deformity of the spine develops; such deformity in most instances can be prevented if the importance of proper posture is conveyed to the patient early and repeatedly.

In about 5 percent of patients with ulcerative colitis extensive spondylitis develops;[11] unlike the peripheral arthritis which accompanies this disease and is described below, the spondylitis tends to progress independent of the activity of the enteric disorder and even after colectomy.[12] Sacroiliitis alone is more common than disease involving additional areas of the spine, and can be demonstrated in nearly 20 percent of patients.[13,14]

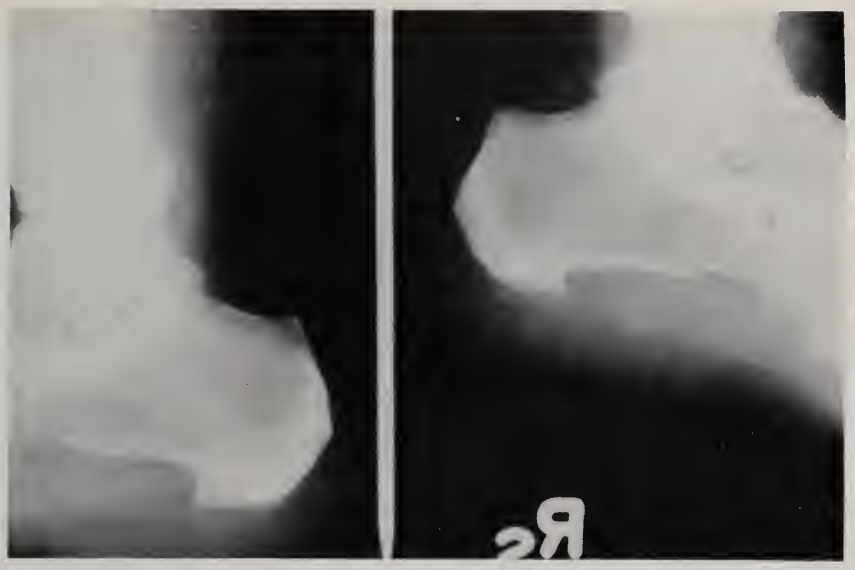


Figure 3.—Roentgenograms of the heels of a patient with Reiter's syndrome, showing calcaneal spurs.

The incidence of spinal arthritis rises with increasing duration of disease, but spondylitis can precede the enteric symptoms.

Reliable estimates of the prevalence of all degrees of spondylitis in patients with psoriasis are not available, but large numbers of cases have been reported and the condition cannot be rare. Sacro-iliitis has been found in about 20 percent of psoriatic subjects.[15]

Figures given for the frequency of spondylitis in Reiter's disease have varied greatly (up to 50 percent). In the large group of postdysenteric cases in Finland, after a 20-year interval spondylitis had developed in at least 10 percent.[16] It is more frequent among patients with chronic or recurrent disease. Once again, involvement of the sacroiliac joints alone often is encountered without evident disease in more cephalad parts of the spine.[16,17]

Sacro-iliitis is thus a finding common to the whole group, but it differs between the two subgroups in that it tends to be more severe with diseases of category 1, and may be asymmetrical with those of category 2.

Patients with spondylitis accompanying colitis, psoriasis or Reiter's syndrome should not be listed on hospital records and other documents as having "ankylosing spondylitis," since that diagnosis is properly applied only to the idiopathic, primary spinal arthritis usually seen among young men. In order to make clear the relationship of secondary spinal disease to the primary process, such patients should be labeled as having "colitic spondylitis," "psoriatic spondylitis," "spondylitis with Reiter's syndrome," or similar terms.

Periostitis and Related Manifestations

Another set of findings which helps to differentiate the spondylo-arthropathies are those produced by periosteal (and sometimes fascial) new bone formation. Particularly in ankylosing spondylitis, periosteal inflammation about the pelvis may produce pain. Roentgenograms made after the disease has been present for several years may show toothbrush-like "feathering" of the margins of the ischial rami and tuberosities or iliac crests. Pelvic periostitis occurs less frequently in the other forms of spondylitis.[3]

Calcaneal spurs, produced by periostitis or by plantar fasciitis or by both, are encountered most frequently in Reiter's disease, especially chronic cases (Figure 3).[18] Because of the venereal associations of that disorder the resultant abnormality has been called "lover's heels." However, spurs are not uncommon in association with ankylosing spondylitis and have been reported with psoriatic spondylitis as well. We have also noted, in many cases of Reiter's syndrome or ankylosing spondylitis, pain or tenderness circumferentially about the heel rather than on the plantar surface. This we suspect also is caused by periostitis, although roentgenograms do not ordinarily show such abnormality. Symptomatic localized periostitis has been described at a number of sites in patients with Reiter's disease.[19]

More specific is the occurrence of fluffy, diffuse periosteal new bone formation along long bones, which sometimes is seen in chronic cases of the diseases of category 2.[18] With psoriatic arthritis, bones of the hands and fingers often are affected, while in Reiter's disease bones of the feet and

toes are more commonly involved. The sites of the manifestation thus parallel the more common location of peripheral joint disease in these two disorders.

Peripheral Arthritis

Another feature separating the two subgroups is the nature of the peripheral arthritis. Ankylosing spondylitis is the only one of these disorders which primarily affects the spine, but even in this disease non-axial joint involvement is common.[10,20] It can take three forms:

1. Arthritis involving one or a few large joints (such as hip, knee, or ankle), which precedes or begins simultaneously with the spinal symptoms in about one-third of cases.[7,8] This usually is self-limited. We have been sufficiently impressed by the frequency of antecedent peripheral large joint disease in ankylosing spondylitis that when a young man presents with an otherwise undiagnosed pauciarthritis, we suspect that spondylitis may become manifest later.
2. Following spondylitis of some duration, arthritis may appear at limb girdle joints (shoulders, hips) and knees.
3. In a small number of patients with ankylosing spondylitis, a peripheral polyarthritis resembling rheumatoid arthritis develops.

Peripheral arthritis appears in at least 15 percent of patients with ulcerative colitis, especially those with severe disease or other extra-intestinal manifestations.[11,12] It is episodic, most attacks not lasting more than two months. Usually only a few joints are involved. In its acute onset and migratory spread, the arthritis may resemble that of rheumatic fever. It differs from rheumatoid arthritis in its predilection for large joints (knees, ankles, elbows), in its asymmetrical involvement of joints, and in the fact that it does not produce deformity. As is true of all the "rheumatoid variants," the peripheral arthritis may precede the primary (in this case, enteric) manifestations of the disease. Peripheral joint symptoms commonly vary in parallel with the severity of the bowel symptoms, and may disappear after colectomy. However, the treatment of colitic arthritis is primarily that of the basic disease, and the joint disorder should never be a reason for colectomy.

A smaller proportion of patients with regional enteritis (Crohn's disease) likewise develop mild arthritis, which may involve small joints of the hands as well as the knees, ankles and other large articulations.[21,22]

Figure 4.—"Sausage toe" produced by interphalangeal joint arthritis, as seen in Reiter's syndrome and psoriatic arthritis.

Involvement of the joints of the limbs in subgroup 2 tends to differ from that just described in that it is more peripheral. Approximately 7 percent of patients with psoriasis are said to develop arthritis.[15] Articulations of the upper limbs are more commonly affected,[23] and the distal interphalangeal joints of the fingers are involved in as many as two-thirds of cases.[1] Since these joints are seldom affected by ankylosing spondylitis, enteric arthropathies, or rheumatoid synovitis, finding inflammation at this site is valuable for differential diagnosis. Marked destruction of the joints of the hands (arthritis mutilans) results from psoriatic arthritis more frequently than from other common arthropathies. Resorption ("whittling") of the terminal phalanges sometimes is seen.

Reiter's disease more often involves the lower limbs: knee, ankle, tarsal and toe joints.[17,24] The "sausage toe" (Figure 4), uniformly swollen along its length because of inflammation at both interphalangeal joints, is characteristic of this syndrome (but also can be seen accompanying psoriasis). Distal interphalangeal joints of fingers may also be affected in this disorder.[3] Episodes of arthritis in Reiter's disease commonly involve a few joints in an asymmetrical manner, and last several months.[25] Articular inflammation may be chronic or recurrent,[26,27] and may be the only presenting symptom, the ocular or genital manifestations having been fleeting or unnoticed. Permanent damage to the joints can occur when the arthritis is chronic.[19,26]

Skin Lesions

A fourth point of difference between the two subgroups of the spondylo-arthropathies is the presence of specific eruptions in subgroup 2. Psoriasis is required for a diagnosis of psoriatic arthropathy, but the skin lesions may be much less evident than the rheumatic disease, or they may appear only after joint disease has developed. On any patient in whom spondylitis or arthritis consistent with psoriatic arthropathy appears, particularly if the distal interphalangeal joints of the fingers are affected, small psoriatic lesions should be carefully sought at the fingernails (frequently pitted on digits where the distal joint is inflamed), scalp, umbilicus and gluteal crease. Atypical forms of psoriasis are said to be more common among those patients who have associated joint disease.[28] The atypical lesions include pustular psoriasis of the palms and soles, which is indistinguishable from the eruption of Reiter's syndrome, even under the microscope.

Distinctive skin lesions are seen on over a quarter of patients with Reiter's disease, changing the classical triad of symptoms—arthritis, urethritis and conjunctivitis—to a tetrad. (These elements need not occur simultaneously, but can be widely separated in time, with a recurring or chronic disease.) Inflammatory, hyperkeratotic skin lesions, called keratoderma blennorrhagicum because they formerly were ascribed to gonorrhea (blennorrhagia), occur most often on the glans penis, but may appear on the palms, soles, or elsewhere. On the uncircumcised penis the hyperkeratotic appearance is lost, and shallow erosions are seen; histologically, this balanitis is identical with the skin lesions elsewhere.[26,29] Balanitis, when it occurs, is a very useful distinguishing feature. Ulcerations of the oral mucosa also occur, but may not be noticed unless specifically sought.

In contrast, specific eruptions are not seen in association with the diseases of category 1. Erythema nodosum and pyoderma gangrenosum sometimes occur with ulcerative colitis.

Other Manifestations

Inflammation of the eyes and aortic root can develop as a manifestation of any of the diseases under discussion. Their presence in a patient with arthritis should lead to consideration of this group of disorders, but is not of much help in distinguishing among the spondylo-arthropathies.

Uveitis or iritis occurs in approximately 10 to 20 percent of patients with ankylosing spondylitis, and may be the presenting symptom.[7,8] Among all patients with ulcerative colitis, uveitis occurs in about 5 to 10 percent, but it is much more common in those with associated spondylitis or peripheral arthritis.[12,14] Such patients also frequently exhibit conjunctivitis.[12] Inflammation of the uveal tract is found less often with regional enteritis.[30] Iridocyclitis is quite common in those cases of Reiter's syndrome in which there are multiple recurrences;[19] it is reported to be more frequent in patients with sacro-iliitis.[31] With this disease keratitis, episcleritis and of course conjunctivitis also are seen.[17] Uveitis occurs only rarely with psoriatic arthritis.[32]

Inflammation and fibrosis at the root of the aorta develop in a significant number of cases of ankylosing spondylitis, producing aortic regurgitation and/or cardiac conduction defects (particularly heart block); the frequency of either of these manifestations is as great as 8 percent.[8,33] At least one case of aortitis in association with colitis and spondylitis has been noted.[34] Aortitis resembling that of ankylosing spondylitis is being reported with increased frequency as a manifestation of chronic Reiter's syndrome;[35] cardiac conduction defects can occur with or without valvular disease. Similarly, aortic regurgitation and heart block have been found in association with psoriatic spondylitis.[28]

While the presence of gastrointestinal symptoms is expected when arthritis is associated with colitis or enteritis, it should be pointed out that Reiter's syndrome can occur following acute enteritis, either epidemic[36] or sporadic.[26] In the latter case it is possible that diarrhea is a manifestation of the Reiter's disease itself.[25]

Laboratory Diagnosis

Other than the roentgenographic features already mentioned which are of diagnostic value (for example, pelvic periostitis in ankylosing spondylitis, whittling of the phalanges with psoriatic arthropathy, calcaneal spur with Reiter's syndrome), laboratory investigations contribute little to the identification of these diseases. The rheumatoid factor (antiglobulin antibody) usually present with rheumatoid arthritis is not commonly found associated with "rheumatoid variants." Other tests may show non-specific abnormalities common to any inflammatory disorder, such as an elevated erythrocyte sedimentation rate.

TABLE 1.—*Differential Diagnosis of Spondylo-arthropathies (Features of Special Value Are in Italic)*

	CATEGORY 1		CATEGORY 2	
	Ankylosing Spondylitis	*Arthritis with Ulcerative Colitis, Regional Enteritis*	*Psoriatic Arthropathy*	*Reiter's Syndrome*
SPONDYLITIS				
Location of syndesmophytes	*anulus fibrosus*	*anulus fibrosus*	anulus and *outer ligaments (>50%)*	anulus and *outer ligaments (>50%)*
Sacro-iliitis	*always*	occurs (20%)	occurs (20%)	occurs (20%)
PERIOSTITIS				
Pelvis	*frequent*	occurs	occurs	occurs
Long bones	none	none	occurs	occurs
Calcaneus	frequent	none	occurs	*frequent*
PERIPHERAL ARTHRITIS				
Characteristic sites	large joints, and lower limb	large joints, and lower limb	*distal interphalangeal,* and upper limb	interphalangeal of toes, other lower limb
SKIN LESIONS	none	occur, not specific*	*specific*	*specific*†
OTHER MANIFESTATIONS				
Uveitis	occurs (15%)	occurs (8%)	rare	*frequent* (>30%)
Aortitis	occurs	rare	occurs	occurs

*Erythema nodosum, pyoderma gangrenosum.
†Keratoderma blennorrhagica, balanitis.

Patients with spondylitis may be found to have unsuspected cardiac conduction defects if electrocardiograms are obtained.

Differentiation from Rheumatoid Arthritis

As their former classification as "variants" of rheumatoid arthritis suggests, these diseases are most often mistaken for rheumatoid arthritis if an error in diagnosis is made. Any of the following features manifested by an adult patient who at first appears to have rheumatoid disease should lead to consideration of the disorders discussed in this paper:

- Arthritis involving a few large joints, and sparing the small joints of the hands, wrists and feet.
- Arthritis involving distal interphalangeal joints of the fingers or interphalangeal joints of the toes.
- Low back pain or stiffness.
- Pain in or tenderness of the heels.
- Uveitis.
- Skin lesions.
- Any recent or chronic abnormality of bowel habits or stools.
- Periostitis on x-ray examination.

It should also be noted that, whereas most patients seeking medical attention for rheumatoid disease are women, ankylosing spondylitis and Reiter's disease (except when it follows epidemic dysentery) are almost exclusively afflictions of men. The spondylitis occurring with psoriasis is also usually seen in men.[3]

Characteristic patterns of clinical manifestations of the spondylo-arthropathies, which aid in their identification, are shown in Table 1. This is presented as a guide giving emphasis to features of diagnostic value, and is not intended as a comprehensive clinical description.

REFERENCES

1. McEwen C, Ziff N, Carmel P, et al: The relationship to rheumatoid arthritis of its so-called variants. Arthritis Rheum 1:481-496, 1958
2. Lawrence JS, Sharp J, Ball J, et al: Rheumatoid arthritis of the lumbar spine. Ann Rheum Dis 23:205-217, 1964
3. McEwen C, DiTata D, Lingg C, et al: Ankylosing spondylitis and spondylitis accompanying ulcerative colitis, regional enteritis, psoriasis and Reiter's disease—A comparative study. Arthritis Rheum 14:291-318, 1971
4. Porrini A, McEwen C, DiTata D, et al: A roentgenologic and clinical study of ankylosing spondylitis and spondylitis accompanying ulcerative colitis, psoriasis and Reiter's disease. Arthritis Rheum 7:338-339, 1964 (abstract)
5. Bunim JJ, Kimberg DV, Thomas LB, et al: The syndrome of sarcoidosis, psoriasis and gout. Ann Intern Med 57:1018-1040, 1962
6. Wright V, Ree WB: The link between Reiter's syndrome and psoriatic arthritis. Ann Rheum Dis 23:12-21, 1964
7. Calabro JJ, Maltz BA: Ankylosing spondylitis. N Engl J Med 282:606-610, 1970
8. Hart DF: Ankylosing spondylitis. Lancet 2:1340-1344, 1968
9. Sigler JW, Bluhm GW, Duncan H, et al: Clinical features of ankylosing spondylitis. Clin Orthop 74:14-19, 1971
10. Polley HF: The diagnosis and treatment of rheumatoid spondylitis. Med Clin North Am 39:509-528, 1955
11. Wilske KR, Decker JL: The articular manifestations of intestinal disease. Bull Rheum Dis 15:362-365, 1965
12. McEwen C: Arthritis accompanying ulcerative colitis. Clin Orthop 57:9-17, 1968
13. Wright V, Watkinson G: Sacro-iliitis and ulcerative colitis. Br Med J 2:675-680, 1965
14. Wright R, Lumsden K, Luntz MH, et al: Abnormalities of the sacro-iliac joints and uveitis in ulcerative colitis. Q J Med 34: 229-236, 1965
15. Wright V, Moll JMH: Psoriatic arthritis. Bull Rheum Dis 21:627-632, 1971
16. Sairanen E, Paronen I, Mahonen H: Reiter's syndrome: a follow-up study. Acta Med Scand 185:57-63, 1969
17. Engleman EP, Weber HM: Reiter's syndrome. Clin Orthop 57:19-29, 1968
18. Peterson CC Jr, Silbiger ML: Reiter's syndrome and psoriatic arthritis; their roentgen spectra and some interesting similarities. Am J Roentgenol 101:860-871, 1967

19. Ford DK: Natural history of arthritis following venereal urethritis. Ann Rheum Dis 12:177-197, 1953

20. Blumberg B, Ragan C: The natural history of rheumatoid spondylitis. Medicine (Baltimore) 35:1-31, 1956

21. Ansell BM, Wigley RAD: Arthritic manifestations in regional enteritis. Ann Rheum Dis 23:64-72, 1964

22. Soren A: Joint affections in regional ileitis. Arch Intern Med 117:78-83, 1966

23. Wright V: Rheumatism and psoriasis. A re-evaluation. Am J Med 27:454-462, 1959

24. Sholkoff SD, Glickman MG, Steinbach HL: The radiographic pattern of polyarthritis in Reiter's syndrome. Arthritis Rheum 14:551-555, 1971

25. Ford DK: Reiter's syndrome. Bull Rheum Dis 20:588-591, 1970

26. Weinberger HW, Ropes MW, Kulka JP, et al: Reiter's syndrome—Clinical and pathologic observations: Long term study of 16 cases. Medicine (Baltimore) 41:35-91, 1962

27. Csonka GW: Recurrent attacks in Reiter's disease. Arthritis Rheum 3:164-169, 1960

28. Reed WB, Wright V: Psoriatic arthritis. *In* Hill AGS (Ed): Modern Trends in Rheumatology, Vol 1. New York, Appleton-Century-Crofts, 1968, pp 375-383

29. Kulka JP: The lesions of Reiter's syndrome. Arthritis Rheum 5:195-201, 1962

30. Daffner JE, Brown CH: Regional enteritis—I. Clinical aspects and diagnosis in 100 patients. Ann Intern Med 49:580-594, 1958

31. Csonka GW: Significance of sacro-iliitis in Reiter's disease. Br J Vener Dis 35:77-80, 1959

32. Reed WB, Becker SW: Psoriasis and arthritis. Arch Dermatol 81:577-585, 1960

33. Weed CL, Kulander BG, Mazzarella JA, et al: Heart block in ankylosing spondylitis. Arch Intern Med 117:800-806, 1966

34. Zvaifler NJ, Weintraub AM: Aortitis and aortic insufficiency in the chronic rheumatic disorders—A reappraisal. Arthritis Rheum 6:241-245, 1963

35. Paulus HE, Pearson CM, Pitts W Jr: Aortic insufficiency in five patients with Reiter's syndrome. A detailed clinical and pathologic study. Am J Med 53:464-472, 1972

36. Noer HR: An "experimental" epidemic of Reiter's syndrome. JAMA 198:693-698, 1966

Practical Tips on Inducing Ovulation (Oligo-Ovulation)

"When do you give human chorionic gonodotropin (HCG); and do you use one dose or two?" We give one injection of 10,000 international units of HCG four days after the last dose of Clomid® in the original sequence; and the HCG is given 48 hours after the last dose of Pergonal® in the second prolonged sequence. In other words, if a dose of Pergonal, or a sequence of Pergonal, has resulted in a 4 plus fern test, we then wait 24 hours and on the following day give the HCG in one dose. The patient is then advised to have intercourse the day after the HCG injection, because ovulation usually occurs within 24 to 30 hours of the HCG.

In an effort to diminish luteal phase insufficiency, we give an additional dose of HCG, 2,000 international units, four days after the first injection of HCG.

Another question that has been asked is, "Should progestational agents or progesterone be used after ovulation induction in this sequence?" Ordinarily we do not, but in patients who have given evidence of being aborters, or habitual aborters, we do begin a progestational agent if the basal body temperature remains elevated 18 consecutive days, from the low point, even before the pregnancy test is positive. This would then be approximately 10 to 14 days after the second HCG injection. We would then use a preparation such as Deluteval®.

Another question is, "Should hydrocortisone be used in any of these sequences?" And I would say, in general, no, but if there are certain patients (and there are a few) in whom the 17 ketosteroids are elevated in the range of 15 to 20, and in whom the diminution in 17 ketosteroids is seen after the administration of hydrocortisone, we do treat these patients with hydrocortisone and with Clomid; and there are certain patients in whom I believe a double-organ defect is present and I think ovulation will only result with this double attack.

Another question, "Should estrogen be given with Clomid?" For years, I advocated the use of estrogen-priming prior to the use of Clomid, but then subsequently gave that up. I would now say that if a patient has had prolonged amenorrhea, say for five or six months, I would prime that patient with estrogen, for example ethinyl estradiol, 0.05 mg twice daily for 20 days, and permit her to have a withdrawal flow, and then try that again. Now, I know that this dose is an ovulation suppressive one and some physicians may object to this and may like to give lower doses. In any event, I think that some priming of the endometrium should be done prior to the sequence in which pregnancy is desired—since, if the endometrium is abnormal or insufficient, abortion may occur. We are also now using a low dose of estrogen (ethinyl estradiol) 0.02 mg from day five through day twelve of the cycle in order to prevent the anti-estrogenic effect of the Clomid on cervical mucus. "How long should one treat patients with these agents (Clomid, Clomid-HCG, Clomid-Pergonal-HCG)? How long should one utilize these sequences before giving up?" I don't know the answer to that question, but I would say usually six to nine cycles should be tried. After all, in a normal couple, where everything is normal, having intercourse four to five times weekly, the woman will only become pregnant in 53 percent of cases within six months. Therefore, I do not believe that the three-cycled treatment of Clomid is adequate, particularly if you suggest that the patient not become pregnant during the first cycle . . . or second cycle if she has had prolonged amenorrhea before. Therefore, we treat our patients for at least six consecutive cycles. I've had one patient become pregnant during the eighth cycle of the Clomid-HCG sequence. I've had another become pregnant on cycle ten, and I think others have had pregnancies occurring as late as cycle twelve.

—ROBERT W. KISTNER, MD, *Boston*

Extracted from *Audio-Digest Obstetrics and Gynecology*, Vol. 20, No. 16, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1930 Wilshire Blvd., Suite 700, Los Angeles, CA 90057.

Refer to: Hopkins GB, Kristensen KAB, Campbell CG: Skeletal scintigraphy—The use of technetium 99M-labeled complexes in the detection of early osseous involvement by metastatic tumors. West J Med 120:448-451, Jun 1974

Skeletal Scintigraphy

The Use of Technetium 99M-Labeled Complexes in the Detection of Early Osseous Involvement by Metastatic Tumors

G. BRUCE HOPKINS, MD, KAI A. B. KRISTENSEN, MD, *and* CHARLES G. CAMPBELL, MD
La Jolla, California

Skeletal scintigraphy using Technetium-99m (^{99m}Tc) complexes was carried out in a series of 332 cancer patients. The results of scintigraphy were compared with the results of roentgenography and with the diagnostic usefulness of serum alkaline and acid phosphatase levels and the presence or absence of bone pain. In 25 percent of cases, lesions were first identified with scintigraphs. When metastastic lesions were present on both scintigraphs and roentgenograms, the number was greater on scintigraphs in 72 percent of cases. Six false negative studies were recorded (1 percent). Sixty percent of patients with early metastasis—that is, those with abnormal scintigraphs and negative roentgenograms—were asymptomatic. Serum alkaline and acid phosphatase levels were normal in 40 percent and 42 percent respectively of those with early skeletal involvement. Skeletal scintigraphy with ^{99m}Tc complexes is superior to other commonly employed techniques used to assess bone metastasis.

SKELETAL SCINTIGRAPHY is of primary importance in detecting early osseous involvement by metastatic tumors. Bone-seeking radiopharmaceuticals localize in the skeleton and reflect variations in regional bone blood flow. As most metastatic tumors elicit a localized reparative reaction with increased bone blood flow, detection is made possible by scintigraphy.

Commonly employed gamma-emitting, bone-seeking radionuclides, including Strontium-85 (^{85}Sr), Fluorine-18 (^{18}F) and Strontium-87m (^{87m}Sr), have certain physical characteristics that preclude optimal scintigraphic studies. The high gamma energies of ^{85}Sr (514 keV) and ^{18}F (511 keV) render high resolution studies difficult or impossible with conventional gamma cameras. The lower gamma energy of ^{87m}Sr (388 keV) is suitable for use with gamma cameras; however, its short half-life of 2.7 hours does not allow sufficient time for blood and soft tissue activity to clear. Because of low count rates obtained with acceptable doses of ^{85}Sr, scintiscans must be done at slow speeds, making routine skeletal surveys

From the Departments of Pathology (Drs. Hopkins and Kristensen); and Radiology (Dr. Campbell); Scripps Memorial Hospital, La Jolla, California.

Submitted December 27, 1973.

Reprint requests to: G. B. Hopkins, MD, Nuclear Medicine Laboratory, Department of Pathology, Scripps Memorial Hospital, Box 28, La Jolla, CA 92037.

TABLE 1.—*Neoplasms Studied—332 Cases*

Site of Origin	*Number of Cases*
Breast	119
Lung	88
Prostrate	48
Lymphoma	22
Gastointestinal	16
Female Genitalia	12
Urinary Tract	11
Myeloma	6
Miscellaneous	10
TOTAL	332

impractical. Attempts to screen asymptomatic patients with ^{85}Sr have generally been limited to the thoracic and lumbosacral spine and pelvis.[1,2]

The recent development of Technetium-99m (^{99m}Tc) polyphosphate[3] and diphosphonate[4] complexes for scintigraphy now permits routine skeletal surveys with images superior to those obtained with other agents. The convenient six hour half-life and low gamma emission of ^{99m}Tc (140 keV) are ideally suited for high resolution studies with either a gamma camera or rectilinear scanner.

This communication reviews the results of skeletal scintigraphic surveys using ^{99m}Tc complexes in a large group of cancer patients. The accuracy and sensitivity of scintigraphy is compared with other techniques commonly employed to assess possible osseous metastasis.

Methods and Materials

This series is made up of 332 patients with biopsy-proven malignant tumors. The primary sites and the number of cases at each of these sites are listed in Table 1. Epithelial lesions of the breast, lung and prostate account for 77 percent of the total studied. The scintigraphs and roentgenograms had all been obtained within three weeks of each other. The presence or absence of bone pain was recorded at the time of scintigraphy.

The clinical records of the patients were reviewed and the serum alkaline and acid phosphatase values, when available, were tabulated. The phosphatase determinations were performed in the hospital laboratory by the method of Bessey, Lowry and Brock.[5]

Fifteen millicuries of ^{99m}Tc-labeled polyphosphate or diphosphonate complex were administered intravenously. The polyphosphate complex was used in 90 patients and the diphosphonate complex in 242 patients. Scintigraphs of comparable quality were obtained with both radiopharmaceuticals. The ^{99m}Tc-diphosphonate complex does offer the advantage of more rapid blood and soft tissue clearance.[4] Patients were encouraged to drink fluids following administration of the dose and to void just before the study. This helps minimize interference from urinary bladder activity.

Figure 1.—Selected views from a normal study on an 18-year-old man. Epyphyseal activity may be seen in both upper extremities. Note that the radiopharmaceutical is distributed in a uniform symmetrical manner.

The instrument used was a Nuclear Chicago High Performance scintillation camera with a 4,000 parallel-hole collimator. The body was surveyed to include the axial skeleton, skull and extremities. A routine study required approximately 14 views and took approximately 50 minutes to complete. The scintigraphs were interpreted independently by two of the authors (GBH and KABK). The criterion for abnormality was either localized increased activity or increased activity over one or more areas when compared with the contralateral side (Figures 1 and 2).

Results

The results of scintigraphy, roentgenography and serum alkaline and acid phosphatase determinations are summarized in Table 2. In 86 cases

Figure 2.—Selected views from a patient with metastatic prostate carcinoma. Metastatic lesions appear as random asymmetrical areas of increased radiopharmaceutical activity.

(26 percent), lesions were present on scintigraphs but not on roentgenograms. Metastasis in all these cases was confirmed by subsequent roentgenographic change, by biopsy of the metastatic site, by relief of osseous pain by radiation therapy, or at autopsy. One hundred and fifty-nine patients had abnormal scintigraphs and metastatic lesions on roentgenograms. Scintigraphs demonstrated more lesions than were evident on the roentgenograms in 115 (72 percent) of these cases. Six patients (1 percent) with lesions on roentgenograms had negative scintigraphic studies.

Serum alkaline phosphatase determinations obtained within two weeks of scintigraphy were available on 186 of the 332 patients. Of these, 26 were excluded because of possible co-existing liver disease as demonstrated by abnormal liver scintigraphy or biopsy, or abnormal liver function tests. Of the remaining patients, 64 (40 percent) with abnormal scintigraphs and negative roentgenograms had normal serum alkaline phosphatase levels. The serum acid phosphatase was normal in 17 (42 percent) of 40 patients with abnormal scintigraphy due to metastatic prostate carcinoma.

Fifty-two (60 percent) of the 86 patients with abnormal scintigraphs and negative roentgenograms were asymptomatic. One or more of the metastatic sites were asymptomatic in 101 patients (63 percent), with lesions present on both scintigraphs and roentgenograms.

TABLE 2.—*Comparison of Scintigraphs with Roentgenograms and Serum Phosphatase Activity*

Scintigraphs	*X-ray Roentgenograms*	*No.*	*Percent*
Abnormal	Positive	159	48
Normal	Negative	81	25
Abnormal	Negative	86	26
Normal	Positive	6	1
Scintigraphs	*Alkaline Phosphatase*	*No.*	*Percent*
Abnormal	Elevated	96	60
Abnormal	Normal	64	40
Normal	Elevated	0	0
Scintigraphs	*Acid Phosphatase*	*No.*	*Percent*
Abnormal	Elevated	23	58
Abnormal	Normal	17	42
Normal	Elevated	0	0

Discussion

In this series of 332 patients, scintigraphy with ^{99m}Tc complexes proved more sensitive than roentgenography in detecting early skeletal metastasis. Moreover, when metastatic lesions were present on both scintigraphs and roentgenograms, the number of lesions was greater on scintigraphs in the majority of cases. The greater diagnostic acuity of scintigraphy is in its ability to reflect early dynamic changes occurring in response to tumor. Roentgenograms show only the net structural change which occurs, both destructive and reparative.[6] Thus, approximately 50 percent of the mineral content must be lost from an area of involvement before a lesion becomes evident on roentgenograms.[7]

Metastatic tumors involving the skull, ribs and sternum were particularly well delineated. We had not noted a similar frequency of lesions at these sites when using ^{18}F[8] and ascribe this to the superior studies obtained with the ^{99m}Tc complexes.

Scintigraphs were interpreted as normal in three patients with metastatic epithelial tumors. One lesion was metastatic from breast while the other two were metastatic from lung. Two were located in vertebral pedicles while the third was in a sacroiliac joint. Each had been lytic by roentgenography and had not elicited sufficient reactive change to permit visualization of abnormal bone blood flow. This number of false negative studies

compares favorably with those reported in other series in which different bone-seeking radionuclides were employed.[2,9,10]

The remaining three patients with false negative scintigraphs had multiple myeloma. Evidence available from ^{85}Sr studies suggests that roentgenograms are superior to scintiscans in detecting myelomas.[9] The paucity of reparative activity associated with most myelomas would account for this observation. The three myeloma patients with abnormal scintigraphs had associated pathologic fractures.

Technetium-99m complexes proved quite effective in locating areas of osseous involvement by malignant lymphoma. All patients with known lymphomatous bone involvement had abnormal scintigraphs. Roentgenograms were negative in five (33 percent) of these patients. Other reports have stressed the superiority of ^{85}Sr scintiscans over roentgenograms in lymphoma.[2,11,12] Our limited experience suggests that the ^{99m}Tc complexes will prove as effective as ^{85}Sr in detecting skeletal lymphoma.

Serum alkaline and acid phosphatase determinations were normal in 40 percent and 42 percent respectively of patients with early skeletal metastasis—that is, those with abnormal scintigraphs and negative roentgenograms. Elevated serum phosphatase was more commonly observed in patients with lesions present on both scintigraphs and roentgenograms. There was no correlation between tumor origin, abnormal scintigraphy and elevation of the serum alkaline phosphatase. The insensitivity of the serum phosphatase renders it of dubious value in assessing early skeletal metastasis. Abnormal scintigraphy in a known cancer patient should obviate the need for these particular biochemical determinations.

While skeletal scintigraphy is a highly sensitive indicator of bone disease, it is not specific for tumors and may yield abnormal results in a variety of conditions. This is particularly true with diseases affecting reparative bone activity. In our experience nonneoplastic conditions causing abnormal scintigraphs include osteomyelitis, rheumatoid spondylitis, recent fractures, Paget's disease, hyperostosis frontalis, arthritides, regional osteoporosis, aseptic necrosis and postoperative healing. Abnormal scintigraphs should always be accompanied by appropriate roentgenograms to rule out other causes of abnormal bone blood flow.

Skeletal scintigraphy with ^{99m}Tc complexes is not only of value in detecting early skeletal metastasis, but should be employed in staging procedures, to confirm suggestive or equivocal roentgenographic findings, to select suitable sites for bone biopsy, to define portals for radiotherapy or to follow the response of tumors to radiation therapy. The localized reduction in radiopharmaceutical uptake that occurs in response to irradiation can prove a helpful guide if metastatic lesions are treated before roentgenographic change occurs.[13] Scintigraphy is also indicated before contemplated radical surgical procedures on known or suspected tumors with a predilection for osseous metastasis.

REFERENCES

1. Galasko CSD: The detection of skeletal matastases from carcinoma of the breast. Surg Gynecol Obstet 132:1019-1024, 1971
2. Gnekow WC, DeNardo GT, Poole GJ, et al: Review of a 5-year experience with the radiostrontium bone scintiscan. Calif Med 117:1-7, Jul 1972
3. Subramanian G, Mcafee JG, Bell EG, et al: ^{99m}Tc-labeled polyphosphate as a skeletal imaging agent. Radiology 102:701-704, 1972
4. Yano Y, McRae J, Van Dyke DC, et al: Technetium-99m-labeled stannous ethane-1-hydroxy-1 1-diphosphonate: A new bone scanning agent. J Nuc Med 14:73-78, 1973
5. Bessey OA, Lowry DH, Brock MJ: A method for the rapid determinations of alkaline phosphatase with five cubic millimeters of serum. J. Biol Chem 164:321-329, 1964
6. Charles MO, Young I, Sklaroff DM: The pathologic basis of the Strontium bone scan. Studies following administration of Strontium chloride Sr-85 and Strontium nitrate Sr-85. JAMA 206: 2482-2488, 1966
7. Rubin P, Ciccio S: Status of bone scanning for bone metastases in breast carcinoma. Cancer 24:1338-1344, 1969
8. Hopkins GB, Kristensen KAB, Blinkenstaff DE: Fluorine-18 bone scans in the detection of early metastatic bone tumors. JAMA 222:813-814, 1972
9. DeNardo GL, Jacobsen SJ, Raventos A: ^{85}Sr bone scan in neoplastic disease. Sem Nucl Med 2:18-30, 1972
10. Blau M, Ganatra R, Bender MA: ^{18}F-Fluoride for bone imaging. Sem Nucl Med 2:31-37, 1972
11. Harbert JC, Ashburn WL: Radiostrontium bone scanning in Hodgkin's disease. Cancer 22:58-63, 1968
12. Weber WG, DeNardo GL, Bergin JJ: Scintiscanning in malignant lymphomatous involvement of bone. Arch Intern Med 121:433-437, 1968
13. Bell EG, Mcafee JG, Constable WC: Local radiation damage to bone and marrow demonstrated by radioisotopic imaging. Radiology 92:1083-1088, 1969

Refer to: Keys TF: Gonococcal antibiotic resistance in Los Angeles. West J Med 120:452-455, Jun 1974

Gonococcal Antibiotic Resistance in Los Angeles

THOMAS F. KEYS, MD
Rochester, Minnesota

One hundred and thirty-five gonococcal isolates collected from Los Angeles in 1972 were studied for antibiotic susceptibility to penicillin, ampicillin, carbenicillin, tetracycline, minocycline, doxycycline and spectinomycin. Only 12 percent of the isolates were sensitive to 0.05 μg per ml of penicillin while 35 percent required at least 0.5 μg per ml for inhibition of growth. The results were slightly better with ampicillin and nearly the same with carbenicillin. Nineteen percent of the isolates required at least 1.0 μg per ml of tetracycline for inhibition of growth and the results were similar with either minocycline or doxycycline. Forty-nine percent were sensitive to 2.0 μg per ml spectinomycin, but 37 percent required at least 8.0 μg per ml for inhibition of growth.

In this study nine of eleven isolates resistant to 1.0 μg per ml of tetracycline were also resistant to both penicillin and spectinomycin. Six came from endocervical sites of female patients who contributed only 37 percent of the total number of isolates studied.

Correlation between the agar dilution and disc diffusion methods was satisfactory with penicillin, but not with ether tetracycline or spectinomycin.

THE ALARMING TREND of antibiotic resistance to Neisseria gonorrhoeae during the past quarter century has focused even more attention on a disease that has reached epidemic proportions in the United States. Since 1970 at least two million cases of gonorrhea have occurred annually. Public health authorities are now recommending 4.8 million units of penicillin plus probenecid for uncomplicated gonococcal infection. In the 1940's, a dose of 160,000 units was considered excessive. Gonorrhea largely occurs in otherwise healthy young adults and single dose parenteral penicillin or a short course of oral tetracycline has been previously successful. As gonococcal antibiotic resistance continues, conventional therapy will no longer be effective. A knowledge of the current antibiotic susceptibility patterns and the pharmacokinetics of the antimicrobials selected are important factors in controlling this disease.

It is impractical for the usual clinical laboratory to perform critical studies on every isolate presumptively identified as N. gonorrhoeae by Gram-stain and oxidase test. Fermentation and antibiotic susceptibility studies are tedious and time-consuming. Moreover, they are not quickly available to the clinician who is anxious to prescribe appropriate chemotherapy at the time the diagnosis is first made.

For this reason we are reporting the antibiotic susceptibility patterns of gonococcal isolates surveyed from the Los Angeles area in 1972.

Materials and Methods

One hundred and thirty-five gonococcal isolates were collected from urethral and endocervical sites of patients seen in the Los Angeles County Health Clinics in the summer of 1972. Eighty-six were from males and 49 from females. The mean age of the patients was 24.5 with a range of 12 to 56 years. All isolates were confirmed as N. gonor-

From the Section of Infectious Diseases, Department of Medicine, VA Hospital, Sepulveda and the University of California, Los Angeles, Center for the Health Sciences.

Submitted October 26, 1973.

Reprint requests to: T. F. Keys, MD, Department of Medicine, Mayo Clinic, Rochester, MN 55901.

rhoeae by Gram-stain, oxidase test and carbohydrate fermentation patterns using cysteine trypticase agar (CTA, Baltimore Biologic Laboratories).

The cultures were preserved for antibiotic susceptibility testing by freezing suspensions in trypticase soy broth (TSB, Baltimore Biologic Laboratories) containing 30 percent agamma horse serum. The isolates were revived by planting thawed suspensions on dextrose starch agar slants (DSA, Baltimore Biologic Laboratories). After incubation for 18 to 24 hours in a 6 percent CO_2 atmosphere at 35°C (95°F), the isolates were resuspended in TSB to give an inoculum of 10^8 colony forming units per ml broth. Barium sulfate standards and absolute colony counts were done to insure accuracy of the inoculum size.

For the agar dilution studies, a 10^{-3} dilution of each isolate was pipetted into the wells of Steers' replicating device. Aliquots were planted on the surface of a DSA pour plate containing the antibiotic to be tested. All antibiotic standards and plates were prepared daily for each experiment. For the disc diffusion studies a 10^{-1} dilution of the isolate was streaked, using a cotton swab on the surface of a Mueller Hinton plate (Baltimore Biologic Laboratories).

Antibiotic standard powders were provided by Bristol Laboratories (penicillin G and sodium ampicillin), Roerig Laboratories (sodium carbenicillin), Lederle Laboratories (tetracycline hydrochloride and minocycline), Pfizer Laboratories (doxycycline) and Upjohn Laboratories (spectinomycin hydrochloride). The dilutions for the penicillins were 3.0, 1.5, 1.0, 0.75, 0.5, 0.25, 0.1, and 0.05 μg per ml. The dilutions for the tetracyclines were 6.0, 4.0, 2.0, 1.0, 0.5 and 0.25 μg per ml. For spectinomycin the dilutions were 16.0, 12.0, 8.0, 6.0, 4.0 and 2.0 μg per ml.

All plates were incubated in a 6 percent CO_2 atmosphere at 35°C (95°F) and read at 24 and 48 hours. No significant changes in the readings were noted. The lowest concentration of antibiotic inhibiting all visible growth constituted the minimal inhibitory concentration (MIC) for the isolate. Control isolates of known susceptibility to penicillin and tetracycline (provided by Center for Disease Control, Venereal Disease Branch, Atlanta, Georgia) were tested with each experiment and always correlated within one dilution of the known value.

For the disc diffusion study, penicillin 2 unit (Baltimore Biologic Laboratories), tetracycline 5 μg (Baltimore Biologic Laboratories) and spectinomycin 30 μg (Upjohn Laboratories) dics were used. All three discs were planted on MH plates containing each isolate to be tested. After incubation in a 6 percent CO_2 atmosphere at 35°C (95°F) the plates were examined at 24 and 48 hours. A steel caliper was used to measure the diameter of zone inhibition. No changes between the readings at 24 and 48 hours were noted.

TABLE 1.—*Comparative Susceptibility of 135 Gonococcal Isolates to Penicillins, Tetracyclines and Spectinomycin*

Antibiotic	*Minimal Inhibitory Concentrations (μg/ml)*						
	0.05	0.1	0.25	0.5	0.75	1.0	>1.0
Penicillin G ...	16	22	50	25	21	1	0
Ampicillin	13	16	97	7	2	0	0
Carbenicillin ...	9	4	14	30	63	8	7
	0.25	0.5	1.0	2.0	4.0	6.0	>6.0
Tetracycline	91	19	14	8	1	0	2
Minocycline	98	19	14	2	1	0	1
Doxycycline	78	22	19	9	5	2	0
	2.0	4.0	6.0	8.0	12.0	16.0	>16.0
Spectinomycin ..	66	11	8	7	35	5	3

Results

Overall Antibiotic Susceptibility Patterns

The susceptibility of the 135 gonococcal isolates to the antibiotic agents tested is illustrated in Table 1. For purpose of discussion, isolates with MICs of 0.5 μg per ml or greater to penicillin, 1.0 μg per ml or greater to tetracycline, and 8.0 μg per ml or greater to spectinomycin were considered insensitive or relatively resistant to the respective antibiotics.

Only 12 percent of the isolates were sensitive to 0.05 μg per ml of penicillin, while 3.5 percent were relatively resistant since their MICs were 0.5 μg per ml or greater of penicillin. Sixty-five percent were susceptible to 0.25 μg per ml or less of

TABLE 2.—*Susceptibility of Eleven Tetracycline-Resistant Isolates to Penicillin and Spectinomycin*

			Minimal Inhibitory Concentrations (μg/ml)		
Id. No.	*Sex*	*Site*	*Tetracycline*	*Penicillin*	*Spectinomycin*
1	♀	Cervix	2.0	0.5	*4.0*
2	♀	Cervix	2.0	0.5	8.0
3	♀	Cervix	2.0	0.5	8.0
4	♂	Urethra	2.0	0.5	12.0
5	♀	Cervix	2.0	0.5	12.0
6	♂	Urethra	2.0	0.5	20.0
7	♀	Cervix	2.0	0.75	12.0
8	♀	Cervix	2.0	0.75	12.0
9	♀	Cervix	4.0	0.75	12.0
10	♂	Urethra	>6.0	*0.25*	>20.0
11	♂	Urethra	>6.0	0.5	>20.0

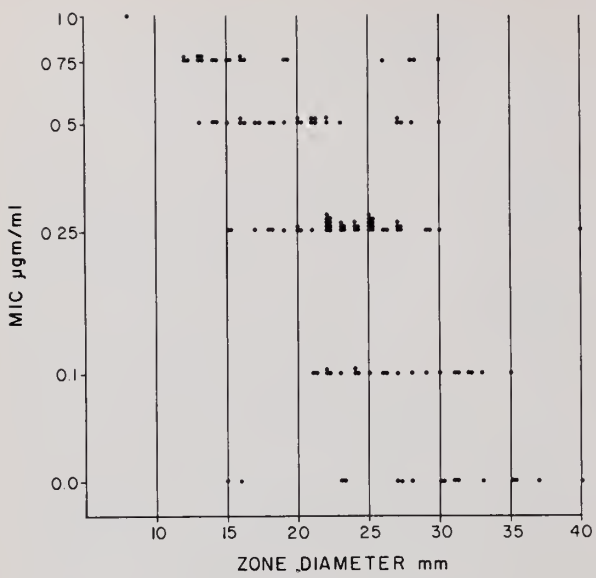


Chart 1.—Comparison of penicillin agar dilution with disc diffusion for 135 isolates of Neisseria gonorrhoeae.

penicillin, 93 percent to the same concentration of ampicillin and 42 percent to carbenicillin. Sixty-seven percent of the isolates were sensitive to 0.25 µg per ml or less of tetracycline and 19 percent required 1.0 µg per ml of tetracycline for inhibition of growth. The results were nearly identical with minocycline and doxycycline. While 49 percent of the isolates were sensitive to 2.0 µg per ml of spectinomycin, 37 percent required at least 8.0 µg per ml for inhibition of growth.

Multiple-drug Resistant Isolates

Seventy-two percent of the isolates with MICs to tetracycline of 1.0 µg per ml or greater had MICs of 0.5 µ per ml or higher to penicillin and to at least 8 µg per ml of spectinomycin. Only four of the fourteen isolates with MICs to tetracycline of 1.0 µg per ml were resistant to both penicillin and spectinomycin. However, of the 11 isolates with MICs to tetracycline of 2.0 µg per ml or greater, nine showed resistance to both (Table 2). Six of these multiple antibiotic-resistant isolates were obtained from endocervical sites of female patients who provided only 36 percent of the total number of isolates collected.

Comparison of Agar Dilution with Disc Diffusion Studies

A regression curve comparing penicillin agar-dilution MIC to the penicillin 2 unit disc-diffusion zone diameter for the isolates is shown in Chart 1. Of 48 isolates with MICs equal to or greater than 0.5 µg per ml, 32 (66 percent) had zones measuring 20 mm or less. Of 87 isolates with MICs equal to or less than 0.25 µg per ml, 76 (87 percent) had zone diameters greater than 20 mm. Of the total 43 isolates with zones 20 mm or less, 32 (74 percent) had MICs to penicillin of 0.5 µg per ml or greater. Of the total 92 isolates with zones greater than 20 mm, 76 (87 percent) had MICs equal to or less than 0.25 µg per ml of penicillin.

Satisfactory correlation did not occur between agar dilution and disc-diffusion results for tetracycline and spectinomycin. Isolates resistant by agar dilution had variable zones of inhibition by disc diffusion testing. For example, only 56 percent of the tetracycline-resistant isolates had low zones of inhibition. The results were even less impressive with spectinomycin.

Discussion

The MICs to penicillin for the gonococcal isolates surveyed in this study were higher than Martin[1] reported in his study of isolates from other metropolitan centers in 1968-69. In that study 65 percent of the isolates had MICs greater than 0.05 units per ml and 15 percent were higher than 0.5 units per ml. In our study 88 percent had MICs higher than 0.08 units per ml (0.05 µg per ml) and 35 percent had MICs higher than 0.4 units per ml (0.25 µg per ml).

The trend toward increasing resistance of gonococci to tetracycline, noted in other studies,[2-4] was also observed with our isolates. Nineteen percent had MICs to tetracycline of 1.0 µg per ml or higher. There were no significant differences among the tetracycline analogues minocycline and doxycycline. The range of susceptibility of the isolates to spectinomycin was similar to that noted by Duncan[5] and Pederson.[6] Thirty-seven percent required at least 8.0 µg per ml for inhibition of growth. How this pattern will be affected after more widespread use of spectinomycin is uncertain. Gonococcal isolates became rapidly resistant to streptomycin following its early effectiveness in treating gonorrhea in the 1940's.

We were favorably impressed with the usefulness of penicillin discs for predicting penicillin-resistant isolates. This has also been noted by other investigators.[7,8] Problems arose, however, in interpreting the tetracycline and spectinomycin disc diffusion data. It is not apparent to us why this was so. Reyn[7] has also reported discrepancies between agar dilution and disc diffusion with tet-

racycline and streptomycin. While penicillin disc testing may be a worthwhile procedure for laboratories supporting venereal disease clinics, we would hesitate to recommend it for laboratories rarely encountering gonococci. Simultaneous agar dilution studies must be done initially and checks from time to time are necessary to insure continued accuracy of the disc method.

Antibiotic resistance is a relative term for the gonococcal isolates reported in this survey, since all were inhibited by penicillin and nearly all by tetracycline and spectinomycin in the concentrations tested. However, it has clearly been shown that isolates susceptible only at the higher ranges tested are associated with more frequent therapy failures.[1,3,5,6,9] Ideally, an antigonorrheal agent should provide a serum concentration that is at least 5 to 10 times the MIC for the isolate.[9,10] Considering the variability of absorption and clearance of antimicrobials, this is often not achieved. However, since intramuscular injection of comparable doses of ampicillin[11] and carbenicillin[12] provide higher serum levels than procaine penicillin, they may be more effective agents since their *in vitro* activity against gonococci is similar to penicillin. Excellent results have been reported in field trials with either of these parenteral preparations.[11,13] Furthermore, the use of 3.5 grams of ampicillin, given in a single oral dose, preceded by one hour with 1.0 gram oral probenecid, has proven highly effective for the treatment of gonococcal urethritis in the Philippines where there is a high prevalence of penicillin-resistant gonococci.[14] This treatment was generally well tolerated by the patients. Less than 2 percent of them had significant gastrointestinal distress and no cases of rash were observed. These semi-synthetic penicillins deserve further clinical evaluation since the administration of greater than 4.8 megaunits procaine penicillin intramuscularly is likely to be painful and may not achieve reliable blood levels.

Despite the fact that tetracyclines are widely used for the treatment of gonorrhea, particularly by private physicians, there are significant disadvantages. First of all, single dose oral therapy can no longer be considered effective.[4,15] Success with multiple dose treatment depends on the reliability of patients to continue to take their medicine despite symptomatic improvement. Secondly, viable gonococci persist in secretions for longer periods increasing the risk of transmission while the patient is on treatment.[16] Lastly, there is a significant cost factor, since the newer tetracyclines, doxycycline and minocycline, are currently more expensive than the recommended doses of tetracycline hydrochloride or procaine penicillin with probenecid.

The multiple drug-resistant patterns of gonococci seen in this study have been noted elsewhere.[7,8,17,18] Why cross-resistance occurs among biologically and chemically unrelated antimicrobials is unknown. Conditioning of heterogeneous clones of gonococci by widespread use of antimicrobials appears to be the most significant factor in stimulating resistance. Sparling[4] has proposed that certain agents provoke a resistance mechanism that blocks their entry into the gonococcal cell. High level resistance may be transmitted to susceptible cells by genetic factors. It is disturbing to consider what the alternatives for therapy will be if the trend of multiple-drug resistance continues. Perhaps in the future we will understand the mechanisms more fully. Meanwhile, it remains important for the clinician to be accurately informed on the trends of antibiotic resistance so that he can prescribe the most effective therapy currently available.

REFERENCES

1. Martin JE Jr, Lester A, Price EV, et al: Comparative study of gonococcal susceptibility to penicillin in the United States, 1955-1969. J Infec Dis 122:459-461, Nov 1970
2. Thayer JD, Samuels SB, Martin JE Jr, et al: Comparative antibiotic susceptibility of Neisseria gonorrhoeae from 1955 to 1964. Antimicrob Agents Chemother, pp 433-436, 1964
3. Martin JE Jr, Lester A, Kellogg DS Jr, et al: In vitro susceptibility of Neisseria gonorrhoeae to nine antimicrobial agents. Appl Micro 18:21-23, Jul 1969
4. Sparling PF: Antibiotic resistance in Neisseria gonorrhoeae. Med Clin NA 56:1133-1144, Sep 1972
5. Duncan WC, Holder WR, Roberts DP, et al: Treatment of gonorrhea with spectinomycin hydrochloride: comparison with standard penicillin schedules. Antimicrob Agents Chemother 1: 210-214, Mar 1972
6. Pedersen AHB, Wiesner PJ, Holmes KK, et al: Spectinomycin and penicillin G in the treatment of gonorrhea. JAMA 20: 205-208, Apr 10, 1972
7. Reyn A, Korner B, Bentzon MW: Effects of penicillin, streptomycin, and tetracycline on N. gonorrhoeae isolated in 1944 and in 1957. Br J Vener Dis 34:227-239, 1958
8. Ronald AR, Eby J, Sherris JC: Susceptibility of Neisseria gonorrhoeae to penicillin and tetracycline. Antimicrob Agents Chemother, pp 431-434, 1968
9. Lucas JB: Gonococcal resistance to antibiotics. South Med Bull 59:22-28, Apr 1971
10. Krook G, Juhlin I: Problems in diagnosis, treatment and control of gonorrheal infections. Acta Derm-Venereal 45:242-253, 1965
11. Keys TF, Halverson CW, Clarke EJ Jr: Single-dose treatment of gonorrhea with selected antibiotic agents. JAMA 210: 857-861, Nov 3, 1969
12. Knudsen ET, Rolinson GN, Sutherland R: Carbenicillin—A new semi-synthetic penicillin active against Pseudomonas pyocyanea. Br Med J 3:75-78, 1967
13. Nelson M: Carbenicillin in the treatment of gonorrhea in males. Health Service Reports 87:762-764, Oct 1972
14. Kvale PA, Keys TF, Johnson DW, et al: Single oral dose ampicillin-probenecid treatment of gonorrhea in the male. JAMA 215:1449-1453, Mar 1, 1971
15. Lassus A: Doxycycline retreatment of gonorrhea in cases with decreased penicillin susceptibility of gonococci. Chemother 15:125-128, 1970
16. Holmes KK, Johnson DW, Floyd TM: Studies of venereal disease. JAMA 202:461-466, Nov 6, 1967
17. Reyn A: Antibiotic sensitivity of gonococcal strains isolated in the South-East Asia and Western Pacific regions in 1961-68. Bull WHO 40:257-262, 1969
18. Phillips I, Ridley M, Rimmer D, et al: In vitro activity of twelve antibacterial agents against Neisseria gonorrhoeae. Lancet 1:263-265, Feb 7, 1970

Specialty Conference

Refer to: Anthony BF, Keys TF, Louie JS, et al: Gonococcal infections—Laboratory, clinical and epidemiological aspects —Teaching Conference, University of California, Los Angeles, and Harbor General Hospital, Torrance (Specialty Conferences). West J Med 120:456-462, Jun 1974

Moderator

BASCOM F. ANTHONY, MD

Discussants

THOMAS F. KEYS, MD
JAMES S. LOUIE, MD
ROBERT N. YOSHIMORI, PhD

This is a transcription of one of the regular teaching conferences in Infectious Diseases held weekly at Harbor General Hospital, Torrance, California. It has been edited by Doctors Jerrold A. Turner, John Z. Montgomerie, Anthony W. Chow, Thomas T. Yoshikawa and Lucien B. Guze.

Gonococcal Infections

Laboratory, Clinical and Epidemiological Aspects

BASCOM F. ANTHONY, MD:* Gonorrhea is a disease of contradictions. Epidemiologically, it is by far the most common reportable infection in this country, although grossly under-reported. Effective treatment and means of control are available, but gonorrhea is currently on the increase. Clinically overt urogenital disease is much more common in men while metastatic infection, particularly arthritis, is predominantly an affliction of women. At the microbiological level, the causative organism was identified almost a century ago, but understanding of basic host-parasite relationships in gonococcal disease is rudimentary.

These contradictions and the changing picture of gonococcal infections are the subject of this symposium. First will be a review of practical means for identifying the gonococcus, followed by consideration of some of the interesting extragenital complications in adult patients and then a brief review of pediatric aspects of gonococcal infection. Finally, we will take up important questions of the modern epidemiology and treatment of gonorrhea.

The Laboratory Diagnosis of Neisseria Gonorrhoeae

ROBERT N. YOSHIMORI, PH D:† The laboratory diagnosis of gonorrhea is a difficult procedure and the best available methods detect only about 50 to 75 percent of infections, a deficiency which further compounds the problem of under-reporting gonococcal infections. Since no single laboratory diagnostic procedure is absolutely reliable, it is appropriate to review currently available techniques.

Direct smears. In Gram stains of male urethral exudates, the observation of Gram-negative intracellular diplococci provides a reasonable presumptive diagnosis of gonorrhea. In women, however, 5 to 10 percent of the organisms observed with the characteristic morphological and staining

*Division of Infectious Diseases, Department of Pediatrics, Harbor General Hospital, Associate Professor of Pediatrics, UCLA School of Medicine.

Reprint requests to: Division of Infectious Diseases, Department of Medicine, Harbor General Hospital, 1000 West Carson Street, Torrance, CA 90509.

†Director of Microbiology Laboratory, Harbor General Hospital, Assistant Professor of Pathology, UCLA School of Medicine.

characteristics may be other than N. gonorrhoeae.[1]

In general, the observation of gonococcus in Gram stains is especially difficult in specimens from the vaginal, cervical and rectal areas. In efforts to increase sensitivity and rapidity in diagnosing gonorrhea, the fluorescent antibody (FA) test has been used with varying success. This has been attempted with direct FA examination of specimens (immediate FA test) or after incubation in broth (delayed FA test). Price[2] reported a 15 percent positive rate in 8,483 women patients with the immediate FA test and a rate of 34 percent with the delayed FA test. The difference in the results indicates that the immediate FA test is not sufficiently sensitive to detect small numbers of gonococci. The increased sensitivity of the delayed test over the immediate FA procedure results from larger numbers of organisms present for at least 20 hours after incubation. Although the FA procedures lack sensitivity and some specificity, in the hands of an experienced worker they are invaluable for the rapid identification of infected contacts. For the average laboratory where only an occasional observation is requested, these tests are probably too cumbersome and unreliable.

Cultivation of the gonococcus. The ultimate method in the laboratory diagnosis of gonorrhea remains the isolation and identification of cultures. After incubation in a CO_2 atmosphere, N. gonorrhoeae can be identified by the oxidative use of glucose but not sucrose, lactose or maltose. In most instances, culture techniques will yield a greater percentage of positive isolates than either the delayed FA test or the Gram stain.

Diagnosing gonorrhea in women from cultures has always been a major problem because organisms from the vaginal and rectal flora commonly overgrow and obscure the gonococcus. Cultures on routine media of these sites in women with suspected gonorrhea can be expected to yield N. gonorrhoeae in about 20 percent of the cases.[2] On the other hand, the recovery rate of gonococcus may be increased about twofold if an inhibitory medium such as Thayer Martin (TM) is used.[3]

Chocolate agar is the base in TM medium and the inhibitory antibiotics are vancomycin, colistin and nystatin.[3] Colistin, however, does not absolutely inhibit all Gram-negative enteric organisms and various non-gonorrheal species are recovered from the medium. Overgrowth and swarming by Proteus is not uncommon and, when it occurs, makes the isolation of the gonococcus virtually impossible. There are other organisms with colonial morphology resembling that of N. gonorrhoeae that are not inhibited by colistin. Among these are Moraxella, Acinetobacter and Neisseria lactamicus, which are frequently found in vaginal and throat cultures. Because of these organisms one should be reluctant to provide a presumptive positive culture report, as has been suggested,[1] even after a positive oxidase test (once thought to be specific for the various Neisseria) or Gram stain has been obtained. In our experience in this laboratory, the frequency of finding N. lactamicus has been responsible for most of this hesitation.

One must be aware that TM medium inhibits a definite population of gonococci. Vancomycin alone inhibits 3 percent of the cultures[4] while 8 percent are inhibited by the complete VCN-TM medium.[5] This suggests that colistin or colistin and vancomycin in combination (synergism) may be responsible for the increased inhibition of growth. Additional studies are needed to substantiate this observation. It is suggested, therefore, particularly when few organisms in pure culture are anticipated (for example with joint fluid, blood and cerebrospinal fluid), that an appropriate non-inhibitory medium (chocolate or starch agar) be inoculated as well as TM medium.

Serologic techniques. Various serological procedures such as hemagglutination,[6] complement fixation,[7] precipitin[8] and fluorescent antibody[9] tests have been investigated with hopes of developing methods comparable to the VDRL (Venereal Disease Research Laboratory test) and FTA (fluorescent treponemal antibody test) used in the diagnosis of syphilis. These efforts have generally fallen short of the goal as the tests appear to have relatively low sensitivity and specificity.

A reason for the failure to develop a satisfactory serological test is probably related to the unstable nature of N. gonorrhoeae. The organism mutates readily on artificial media and at least four virulence-related colony types are recognized.[10] Due to this instability, specific antiserum or antigen is difficult to obtain. It is also conceivable that N. gonorrhoeae may be antigenically weak and does not provoke a protective antibody response. This would be consistent with the observation that patients can be reinfected many times without clinical evidence of immunity.

Thus, there is no completely satisfactory method for the laboratory diagnosis of gonorrhea. However, Swanson[11] has recently observed hair-like pili associated with virulence in the

gonococcus. In the near future, it may be possible to use this antigen for the development of specific, diagnostic antiserum or sensitive serological techniques.

Extragenital Manifestations of Gonococcal Disease

JAMES S. LOUIE, MD:* The extragenital manifestations of gonococcal infection are thought to be related to hematogenous spread. Following infection and infiltration of mucosal or non-stratified epithelium, the replicating gonococcus overwhelms the local tissue defenses and disseminates. Early after contact a systemic response to the bacteremia may occur with fevers, chills, sweats, embolic skin lesions and polyarthritis with tenosynovitis; the gonococcus may be cultured from the blood or a genital site but rarely from the joint fluid or the skin lesions (first or bacteremic stage). Alternatively, there may be no clinically detectable bacteremic phase; the patient may present with a longer incubation time since contact and a localized infection in a single joint (second or septic joint stage). Organisms can be cultured from the joint fluid alone but not from peripheral blood. These concepts were suggested by Keiser[12] who documented the presentation and course of 30 patients with gonococcal arthritis. It is as if, in the bacteremic phase, the sparse number of organisms in the metastatic sites precludes any successful culture. Even so, with a longer incubation period, sufficient bacterial replication occurs to permit a positive culture. Although these concepts are useful guides, clinical observation of gonococcal disease has not always been easily categorized into the separate groupings,[13] and it is prudent to culture all available sites, genital and extragenital, when complicating gonorrheal disease is suspected.

Let us then turn to a more complete clinical discussion of the common and serious forms of gonococcal dissemination.[14]

Gonococcal arthritis. Arthritis is the most common sign of dissemination, occurring in 90 percent of patients according to a recent review.[15] Yet documentation remains difficult. Even in the septic joint phase, when the synovial fluid is purulent, only 50 percent of cultures are positive for the organism. One report has demonstrated successful recovery of organisms on special media to support L-forms,[16] suggesting that the failure to recover gonococcus may possibly be related to cell wall-deficient organisms in some cases. A therapeutic trial of penicillin may be necessary to substantiate the diagnosis.[17]

Perihepatitis. Perihepatitis (Curtis-Fitz-Hugh Syndrome) usually occurs in women presenting with sudden right upper quadrant pleuritic pain and, rarely, a friction rub like "the crunching of new snow."[18] Dissemination is thought to occur via the open fallopian tubes and paracolic gutter, but more recent reports of men presenting with perihepatitis have suggested a hematogenous or lymphatic spread.[19]

Cutaneous manifestations. Skin lesions, particularly in a pariarticular distribution, are common. The lesions may present as a macule with an erythematous or hemorrhagic base or a tender but not painful pustule or actual bullus. With time, the lesions develop a dirty grey necrotic center with crusting, and eventual post-inflammatory hyperpigmentation. Documentation of organisms in these lesions is difficult. Gram stains of pustular fluid or biopsy material are said to be occasionally helpful[20] but more encouraging are reports of gonococci shown in fluid and biopsy material by direct fluorescent antibody techniques.[21]

Other infections. Fortunately, the complications of endocarditis and meningitis are rare. Endocarditis as described in the 1940's approached the severity of a staphylococcal endocarditis[22] with an average survival of five weeks. Embolic phenomena were common, especially to the kidneys and occasionally to large vessels. Curiously, the fever was often double quotidian in pattern, a reportedly diagnostic point.[23]

Meningitis is also a serious but rare complication. Clinically it cannot be distinguished from meningitis related to Neisseria meningitidis.[24] Sugar fermentation tests of the organism isolated from the cerebrospinal fluid as well as culture from the genital sites, are important means of differentiation.[25,26]

Pediatric Aspects of Gonococcal Disease

BASCOM F. ANTHONY, MD: Pediatricians and other physicians who care for children are most likely to encounter gonococcal infections in their sexually active, adolescent patients. Since Dr. Keys will consider gonorrhea in these persons, this discussion will be limited to gonococcal disease in the infant and pre-adolescent child.

Gonococcal infections in children may take

*Division of Rheumatology, Department of Medicine, Harbor General Hospital, Assistant Professor of Medicine, UCLA School of Medicine.

many of the forms seen in adults, including urethritis, vaginitis and metastatic complications, notably arthritis. The gonococcus was responsible for 5 percent of septic joint infections in a recent series from a large pediatric service.[27] Gonococcal arthritis may occur in any age group, including infancy and the pre-school-age years,[27,28] and has many similarities to the arthritis-synovitis syndrome which Dr. Louie has described in older persons. The two forms of gonococcal disease which are seen most in childhood are vulvovaginitis and neonatal gonococcal conjunctivitis.

Gonococcal vulvovaginitis. Gonorrheal vulvovaginitis in pre-adolescent girls is characteristic because of the unique susceptibility of the immature vaginal epithelium to invasion by the gonococcus. In contrast to gonorrhea, which is commonly subclinical in the mature woman, symptoms of vulvovaginitis in children are particularly distressing and include marked irritation and distinctly abnormal, creamy vaginal discharge.[29]

Gonococcal ophthalmia neonatorum. Because of the tendency of untreated neonatal gonococcal ophthalmia to result in corneal damage and blindness, this can be a particularly devastating infection. Although large numbers of cases have not been reported from a single center, several reports clearly indicate a significant increase in recent years.[30,31] Undoubtedly this increase would have been much greater in the absence of prophylaxis. The instillation of 1 percent silver nitrate eyedrops, the usual form of prophylaxis, has not been given strictly controlled evaluation, but considerable indirect evidence attests to the efficacy of this practice. This evidence includes a sharp drop in gonococcal ophthalmia when silver nitrate prophylaxis was first introduced by Credé,[32] a decline in the role of the gonococcus as a cause of blindness in the United States following the passage of laws requiring prophylaxis[33] and the sudden reappearance of gonococcal ophthalmia in one nursery which temporarly discontinued the Credé procedure.[34] The frequency with which silver nitrate is followed by chemical conjunctivitis led in the 1940's to the introduction of alternative prophylaxis with topical antibiotics. Although these measures were accompanied by less chemical conjunctivitis,[35-37] none proved superior to silver nitrate in preventing gonococcal infection and there was increasing concern about sensitization of the patient, particularly with topical penicillin. Accordingly, topical antibiotic prophylaxis never gained the wide acceptance of silver nitrate.[33]

Gonococcal ophthalmia is most often misdiagnosed as chemical conjunctivitis. Classically it appears in the first five days of life[30] but the appearance of signs of conjunctivitis may be significantly delayed beyond this time.[38] Additional delays in recognition have been attributed to empirical treatment with topical antibiotics, combined with the failure to make appropriate bacteriological studies.[38] Therefore, the diagnosis should be strongly considered whenever purulent conjunctivitis develops in early life. It should be stressed that gonococcal eye infections at *any* age may produce permanent corneal damage.[39]

Epidemiology of Gonococcal Infections in Children. The usual maternal source of the gonococcus in neonatal ophthalmia is clear, but the mode in which children acquire the gonococcus is less certain. In one large series of 180 gonococcal infections in children, it was concluded that all children one year and older were infected by direct sexual exposure.[40] In contrast, one-half of a smaller group of children were thought to have acquired the organism from infected adults indirectly by intermediary objects or by direct, non-sexual exposure.[41] The most compelling evidence for non-sexual transmission can be found in older reports of nursery outbreaks of gonococcal infection. A striking example is the occurrence of infection, particularly arthritis, in one-third of 182 newborn infants in a Philadelphia nursery in 1924 within a sharply circumscribed period of six weeks.[42] Although the author of this report suspected that the epidemic was spread by contaminated fomites, it seems more likely that the hands of hospital personnel may have been the vehicle.

Regardless of how gonococcal infections are spread to them, it is clear that infants and children are in jeopardy whenever gonorrhea is prevalent in their adult companions.

Epidemiology and Management of Gonorrhea

THOMAS F. KEYS, MD:* Despite the availability of effective chemotherapy, gonococcal infections have reached epidemic proportions in the United States.[43] Last year 700,000 cases were reported, compared to 250,000 cases in 1952. These figures understate the problem, however, since most

*Division of Infectious Diseases, Department of Medicine, Sepulveda Veterans Administration Hospital, Assistant Professor of Medicine, UCLA School of Medicine. Current Address: Mayo Clinic, Rochester, MN 55901.

cases of gonorrhea are not reported. Conservative estimates by public health authorities place the figure above two million cases annually since 1970. The prevalence rates of reported gonorrhea vary in our large cities. Last year in Atlanta, the rate was 2,500 cases per 100,000 population, while our reported rate in Los Angeles was 500 per 100,000 population. Superficially, one might conclude that gonorrhea is five times more rampant in Atlanta than in Los Angeles. However, this is most likely due to more accurate case reporting in Atlanta, where the Venereal Disease Branch of the United States Public Health Service is located.

During the Viet Nam conflict, our military also had an alarming rate of venereal disease. In 1970, 20 to 25 percent of soldiers stationed in Viet Nam, Korea and Thailand were reported to have venereal disease, the leading form being gonorrhea.

Young adults between the ages of 15 and 29 are at greatest risk of contracting gonorrhea. Their permissiveness and casual attitude about venereal disease contribute to the problem. As Dr. Louie has pointed out, complications of gonorrhea may be serious and the public must be made more aware of them. Furthermore, community physicians, who care for most patients with gonorrhea in our country, must be knowledgeable about the current methods of diagnosis, therapy and follow-up.

Because gonococcal infection in heterosexual men is usually acute, symptomatic and self-limited, they do not constitute the large reservoir of transmissible gonococci that women potentially do. However, recent studies have shown that significant numbers of heterosexual as well as homosexual men may also carry gonococci without symptoms. Eradication of the gonococcal reservoir from asymptomatic carriers is a difficult task. At present, serologic tests are neither specific nor sensitive enough to detect asymptomatic gonorrhea. A large scale program to obtain cultures regularly from all sexually active individuals is not yet practical.

On the other hand, when gonococcal infection is suspected, a concentrated effort must be made to isolate the gonococcus from a likely site. The urethra and endocervix have always provided excellent sources for gonococci. Cultures of the anorectum and oral pharynx are also useful if symptoms occur in these areas, if there is a history of rectal or oral intercourse or if one suspects disseminated gonococcal infection. Although culture of gonococcic skin lesions rarely yields viable organisms, Gram stain or direct immunofluorescent studies are worthwhile procedures.

A specimen must be promptly cultured on appropriate medium in a CO_2-enriched environment. Ideally, the time interval between collection and incubation should not be longer than ten minutes. The culture plates must be warmed to room temperature before they are inoculated. As noted by Dr. Yoshimori, it is wise to plant specimens on both Thayer-Martin and chocolate agar since the antibiotic inhibitors of the former may prevent growth of fastidious gonococci.

Antibiotic resistance. The phenomenon of gonococcal antimicrobial resistance has been observed since the introduction of sulfonamide therapy for gonorrhea in the 1930's. A strong, progressive insensitivity of gonococci to penicillin has occurred since the early 1950's. While 99 percent of isolates surveyed in 1950 were susceptible to very low concentrations of penicillin *in vitro* (0.05 units per ml), in 1969 this was true for only 30 percent of more recent isolates.[44] In a survey of 135 isolates which we collected in Los Angeles last year, only 12 percent were susceptible to this concentration of penicillin (unpublished data).* Thirty-five percent had minimal inhibitory concentrations (MICs) to penicillin of 0.5 μg per ml or higher. We consider these isolates insensitive or relatively resistant to levels of penicillin achievable by conventional single-dose therapy. Similar patterns of resistance have also been observed with the tetracyclines,[45] agents widely used by private physicians for gonococcal therapy. In our survey, 19 percent of the isolates had MICs for tetracycline of 1.0 μg per ml or greater. For optimal anti-gonococcal therapy, a serum concentration five to ten times the MIC for the isolate is desirable.[46] This is often not achieved with the oral tetracyclines.

We have also studied the susceptibility of gonococci to spectinomycin hydrochloride, a new aminoglycoside that has shown promise in clinical field trials.[47] Although the majority of isolates we tested were susceptible to relatively low concentrations of spectinomycin, 37 percent required at least 8.0 μg per ml for inhibition of growth. Whether this pattern will change with the more widespread use of spectinomycin is uncertain. One recalls with dismay the rapid emergence of gono-

*Published elsewhere in this issue of THE WESTERN JOURNAL OF MEDICINE.

cocci resistant to streptomycin following its early clinical effectiveness against gonorrhea in the 1940's.

Conditioning of a heterogenous gonococcal population to sublethal concentrations of antibiotic leads to the development of resistant isolates that may be carried to sexual partners. This may occur when inadequate therapy is given either for therapy or for prophylaxis when the patient is in fact an asymptomatic carrier.

Isolates resistant *in vitro* to one agent frequently exhibit multiple drug resistance. In our studies the resistance pattern appears to have some bearing on susceptibility to tetracycline. That is, tetracycline-resistant isolates tended also to be resistant to penicillin and spectinomycin, but the reverse was not necessarily true. Nine of 11 isolates with MICs for tetracycline of 2.0 μg per ml or greater were resistant to both penicillin and spectinomycin. It was disturbing to note that six of the nine isolates came from endocervical sites of women who contributed only 37 percent of the total isolates surveyed.

Treatment. Although oral tetracycline is a widely used therapy for gonorrhea, it has significant limitations. First of all, the MICs of most gonococci for tetracycline are higher than for penicillin and consequently clinical failures are more common, particularly with single-dose, oral therapy.[48] Second, viable gonococci persist for longer periods after therapy is started, allowing for transmission to occur.[49] Third, absorption following peroral therapy may be variable and the drug poorly tolerated. Fourth, successful treatment depends on the patient being self-reliant enough to follow a prescribed course of therapy. And finally, the tetracyclines, particularly the newer analogues, are more expensive than penicillin. In our studies, as well as those reported by others,[46] there has been no *in vitro* superiority of one tetracycline derivative to another.

A new approach to the therapy of gonorrhea is the use of sulfonamide in combination with trimethoprim. These agents inhibit sequential steps of folic acid metabolism to act additively or synergistically against gonococci. Field trials have shown this to be an effective combination.[50] However, multiple-dose, oral therapy is required and the dosage of each agent has not been established. Furthermore, it is not known if trimethoprim will prevent the re-emergence of sulfonamide-resistant gonococci.

The therapy of choice for gonorrhea remains penicillin. However, megaunit dosage with probenecid to sustain serum levels is now necessary to achieve acceptable cure rates.[51] For uncomplicated gonococcal urethritis or cervicitis a single dose of 4.8 million units of aqueous procaine penicillin G (2.4 million units in each buttock) with 1 gram of oral probenecid is recommended. Alternative therapy with 3.5 grams of oral ampicillin trihydrate and probenecid may be used. We were favorably impressed with this combination for the treatment of "penicillin-resistant" gonorrhea among servicemen in the Philippine Islands.[52] For penicillin-allergic patients, a dose of 2 to 4 grams of spectinomycin hydrochloride given intramuscularly is recommended. The dose schedule for oral tetracycline hydrochloride is 1.5 grams initially and 500 mg every six hours for four days.

These dosage regimens also appear effective against oral-pharyngeal and anorectal gonorrhea and for treating the asymptomatic carrier. If therapy fails, one can usually achieve a cure by repeating the dose of the original antibiotic or using an alternative agent.

For disseminated gonococcal infection it is our practice to admit the patient to hospital and administer 6 to 12 million units of aqueous penicillin G daily by intravenous infusion. Therapy is continued for 72 hours beyond the disappearance of symptoms and signs. Oral tetracycline hydrochloride, 1.5 grams initially and 500 mg every six hours, may be used in penicillin-allergic patients.

REFERENCES

1. Thayer JD: Neisseria gonorrhoeae (Gonococcus), chap 9, *In* Blair JE, Lennette EH, Turant JP (Eds): Manual of Clinical Microbiology, Am Soc for Microbiology, Bethesda, Md, 1970, pp 82-87

2. Price EV: Field evaluation of the fluorescent antibody technique in the detection of the gonococcus in the female, *In* Digest of Proceedings: Fourteenth Annual Symposium on Recent Advances in the Study of Venereal Diseases, Houston, Texas, Jan 24-25, 1964, pp 15 (US Department of Health, Education and Welfare, Public Health Service)

3. Thayer JD, Martin JE Jr: Improved medium selective for cultivation of N. gonorrhoeae and N. meningitidis. Public Health Reports 81:559-562, June 1966

4. Reyn A: Recent developments in the laboratory diagnosis of gonococcal infections. Bull WHO 40:245-255, 1969

5. Cross RC, Hoger MB, Neibaur R, et al: VCN-Inhibited strains of Neisseria gonorrhoeae. HSMHA Health Rep 86:990-992, 1971

6. Ward ME, Glynn AA: Human antibody response to lipopolysaccharides from Neisseria gonorrhoeae. J Clin Path 25:56-59, Jan 1972

7. Schmale JD, Danielsson DG, Smith JF, et al: Isolation of an antigen of Neisseria gonorrhoeae involved in the human immune response to gonococcal infection. J Bacteriol 99:469-471, Aug 1969

8. Reising G, Kellogg DS Jr: Detection of gonococcal antibody. Proc Soc Exp Biol Med 120:660-663, Dec 1965

9. Welch BG, O'Reilly RJ: An indirect fluorescent-antibody technique for study of uncomplicated gonorrhea—I. Methodology. J Infect Dis 127:69-76, Jan 1973

10. Kellogg DS Jr, Peacock WL Jr, Deacon WE, et al: Neisseria gonorrhoeae—1. Virulence genetically linked to clonal variation. J Bacteriol 85:1274-1279, June 1963

11. Swanson J, Kraus SJ, Gotschlich EC: Studies on gonococcus

infection—1. Pili and zones of adhesion: their relation to gonococcal growth patterns. J Exp Med 134:886-906, Oct 1971

12. Keiser H, Ruben FL, Wolinsky E, et al: Clinical forms of gonococcal arthritis. N Engl J Med 279:234-240, Aug 1, 1968

13. Brandt K, Cathcart E, Cohen A: Conococcal arthritis: Two clinical forms? Arthritis Rheum 16:115-116, Jan-Feb 1973

14. Kraus SJ: Complications of gonococcal infection. Med Clin North Am 56:1115-1125, Sep 1972

15. Holmes KK, Counts GW, Beaty HN: Disseminated gonococcal infection. Ann Intern Med 74:979-993, Jun 1971

16. Holmes KK, Gutman LT, Belding ME, et al: Recovery of Neisseria gonorrhoeae from "sterile" synovial fluid in gonococcal arthritis. N Engl J Med 284:318-320, Feb 11, 1971

17. Cooke CL, Owen DS, Irby R, et al: Gonococcal arthritis. A survey of 54 cases. JAMA 217:204-205, Jul 12, 1971

18. Fitz-Hugh T Jr: Acute gonococcic peritonitis of the right upper quadrant in women. JAMA 102:2094-2096, Jun 23, 1934

19. Kimball MW, Knee S: Gonococcal perihepatitis in a male. The Fitz-Hugh-Curtis Syndrome. N Engl J Med 282:1082-1084, May 7, 1970

20. Abu-Nassar H, Hill N, Fred HL, et al: Cutaneous manifestations of gonococcemia. A review of 14 cases. Arch Intern Med 112:731-737, Nov 1963

21. Barr J, Danielsson D: Septic gonococcal dermatitis. Br Med J 1:482-485, Feb 27, 1971

22. Williams RH: Gonococcic endocarditis. Study of 12 cases, with 10 postmortem examinations. Arch Intern Med 61:26-38, Jan 1938

23. Futcher PH: The double quotidian temperature curve of gonococcal endocarditis—A diagnostic aid. Am J Med Sci 119: 23-27, Jan 1940

24. Swierczewski JA, Mason EJ, Cabrera PB, et al: Fulminating meningitis with Waterhouse-Friderichsen syndrome due to neisseria gonorrhoeae. Am J Clin Pathol 54:202-204, Aug 1970

25. Taubin HL, Landsberg L: Gonococcal meningitis. N Engl J Med 285:504-505, Aug 1971

26. Keys TF, Hecht RH, Chow AW: Endocervical Neisseria meningitides with meningococcemia. N Engl J Med 285:505-506, Aug 1971

27. Nelson JD: The bacterial etiology and antibiotic management of septic arthritis in infants and children. Pediatrics 50:437-440, Sep 1972

28. Fink CW: Gonococcal arthritis in children. JAMA 194: 237-238, Oct 1965

29. Altchek A: Pediatric vulvovaginitis. Pediatr Clin North Am 19:559-580, Aug 1972

30. Barrett-Connor E: Gonorrhea and the pediatrician. Am J Dis Child 125:233-238, Feb 1973

31. Snowe RJ, Wilfert CM: Epidemic reappearance of gonococcal ophthalmia neonatorum. Pediatrics 51:110-114, Jan 1973

32. Credé KSF: Reports from the obstetrical clinic in Leipzig. Prevention of eye inflammation in the newborn. Am J Dis Child 121:3-4, Jan 1971

33. Barsam PC: Specific prophylaxis of gonorrheal ophthalmia neonatorum. N Engl J Med 274:731-734, March 1966

34. Mellin GW, Kent MP: Ophthalmia neonatorum: Is prophylaxis necessary? Pediatrics 22:1006-1015, Nov 1958

35. Franklin HC: Prophylaxis against ophthalmia neonatorum. Clinical comparison of penicillin and silver nitrate: A preliminary report. JAMA 134:1230-1235, Aug 1947

36. Davidson HH, Hill JH, Eastman NJ: Penicillin in the prophylaxis of ophthalmia neonatorum. JAMA 145:1052-1055, Apr 1951

37. Christian JR: Comparison of ocular reactions with the use of silver nitrate and erythromycin ointment in ophthalmia neonatorum prophylaxis. J Pediatr 57:55-60, Jul 1960

38. Schofield CBS, Shanks RA: Gonococcal ophthalmia neonatorum despite treatment with antibacterial eye-drops. Br Med J 1:257-259, Jan 1971

39. Thatcher RW, Pettit TH: Gonorrheal conjunctivitis. JAMA 215:1494-1496, Mar 1971

40. Branch G, Paxton R: A study of gonococcal infections among infants and children. Public Health Reports 80:347-352, Apr 1965

41. Shore WB, Winkelstein JA: Nonvenereal transmission of gonococcal infections to children. J Pediatr 79:661-663, Oct 1971

42. Cooperman MB: Gonococcus arthritis in infancy. A clinical study of 44 cases. Am J Dis Child 33:932-948, Jun 1927

43. "Today's VD Control Problem"—A joint statement of the Am Soc Health Assoc, Am Venereal Disease Assoc and the Assoc of State and Territorial Health Officers, 1973

44. Martin JE Jr, Lester A, Price EV, et al: Comparative study of gonococcal susceptibility to penicillin in the United States, 1955-59. J Infec Dis 122:459-461, Nov 1970

45. Sparling PF: Antibiotic resistance in Neisseria gonorrhoeae. Med Clin North Am 56:1133-1144, Sep 1972

46. Lucas JB: Gonococcal resistance to antibiotics. South Med J 59(2):22-28, Apr 1971

47. Pedersen AHB, Wiesner PJ, Holmes KK, et al: Spectinomycin and penicillin G in the treatment of gonorrhea—A comparative evaluation. JAMA 220:205-208, Apr 1972

48. Wiesner PJ, Holmes KK, Sparling PF, et al: Single doses of methacycline and doxycycline for gonorrhea: A cooperative study of the frequency and cause of treatment failure. J Infect Dis 127:461-466, Apr 1973

49. Holmes KK, Johnson DW, Floyd TM: Studies of venereal disease—1. Probenecid-procaine penicillin G combination and tetracycline hydrochloride in the treatment of "penicillin-resistant" gonorrhea in men. JAMA 202:461-466, Nov 1967

50. Csonka GW, Knight GJ: Therapeutic trial of trimethoprim as a potentiator of sulfonamides in gonorrhea. Br J Vener Dis 43:161-165, Sep 1967

51. Holmes KK, Karney WW, Harnisch JP, et al: Single-dose aqueous procaine penicillin G therapy for gonorrhea—Use of probenecid and cause of treatment failure. J Infect Dis 127:455-460, Apr 1973

52. Kvale PA, Keys TF, Johnson DW, et al: Single oral dose ampicillin-probenecid treatment of gonorrhea in the male. JAMA 215:1449-1453, Mar 1971

Refer to: Wilson AF, Galant SP: Recent advances in the pathophysiology of asthma (Medical Progress). West J Med 120:463-470, Jun 1974

Medical PROGRESS

Recent Advances in the Pathophysiology of Asthma

ARCHIE F. WILSON, MD, PhD, *and* STANLEY P. GALANT, MD, *Irvine, California*

THE CLASSIC CONCEPT OF BRONCHIAL ASTHMA as a disease of solely immunologic nature cannot explain many phenomena frequently associated with asthma: hyperresponsiveness of the tracheobronchial tree to chemical mediators and irritants; exacerbations produced by certain respiratory infections, emotional and physical factors; the presence of eosinophilia; decreased bronchodilator response to epinephrine in patients with status asthmaticus; and the therapeutic response of agents which restore beta adrenergic responsiveness. In addition, a large number of asthmatic patients have no evidence of any reaginic (immunoglobulin E) abnormality.

Neuropharmacology

Beta Adrenergic Blockade Theory[1]

The tone of the airways is modulated in large part by the balance of adrenergic and cholinergic activity upon bronchial smooth muscle (Table 1). Adrenergic stimulation leads to bronchodilatation if beta receptors (dominant in lung) are activated and to bronchoconstriction when alpha receptors are stimulated, while cholinergic stimulation results in bronchoconstriction. Recently, the beta adrenergic receptor has been further dissected into beta 1 (cardiac stimulator) and beta 2 (bronchodilator and vasomotor depressor) sub-groups.[2] This has important therapeutic implications since use of drugs which selectively cause bronchodilatation has obvious advantages.

In the early 1960's Szentivanyi advanced the theory of beta adrenergic blockade as a possible unifying pathogenic mechanism in asthma.[1] In brief, this theory proposes that many of the stimuli which result in the clinical syndrome of asthma do so by causing release of potent chemical mediators of inflammation (discussed further below) such as the kinins, slow reacting substance of anaphylaxis (SRS-A), histamine, serotonin and acetylcholine. These mediators, in turn, result in both bronchoconstriction and secretion of epinephrine as a homeostatic response. If beta adrenergic receptors are normally responsive, activation of these by epinephrine will balance concurrent alpha adrenergic and cholinergic receptor stimulation and airway patency will be maintained. However, if beta receptors are defective, bronchoconstriction is favored. Through experimentation first with hypothalamically imbalanced guinea pigs and later with mice challenged with Bordetella pertussis, Szentivanyi presented evidence

From the Departments of Medicine and Pediatrics, University of California, Irvine, California College of Medicine.

Reprint requests to: A. F. Wilson, MD, PhD, Department of Medicine, University of California, Irvine, California College of Medicine, Irvine, CA 92668.

TABLE 1.—*Pharmacology of Autonomic Modulation*

Reactant	*Site of Action*	*Cyclic Nucleotide Effect*	*Mast Cell Mediator Release*	*Bronchial End Organ Response*	*Blocker*
Isoproterenol	Beta Adrenergic Receptor-Adenyl Cyclase Stimulation	↑CAMP	Inhibited	Bronchodilatation	Propanalol
Epinephrine*	Beta Adrenergic Receptor-Adenyl Cyclase Stimulation	↑CAMP	Inhibited	Bronchodilatation	Propanalol
Norepinephrine	Alpha Adrenergic Receptor ?ATPase Stimulation	↓CAMP	Enhanced	Bronchoconstriction	Phentolamine
Theophylline	Phosphodiesterase Inhibition	↑CAMP	Inhibited	Bronchodilatation	..
Acetylcholine and analogues	Cholinergic Receptor-?Guanyl Cylase Stimulation	↑CGMP	Enhanced	Bronchoconstriction	Atropine

*Also has adrenergic activity but, in the lung, beta is dominant.

which demonstrated that creation of autonomic imbalance (decreased beta adrenergic receptor function with normally intact alpha adrenergic and cholinergic receptor function) could produce many of the immunologic, pharmacologic and biochemical abnormalities noted in asthmatic patients.[1]

The evidence for generalized beta blockade in asthma includes metabolic, pulmonary and hematologic changes. *Metabolic* studies have demonstrated less elevation of serum glucose, lactate and pyruvate following administration of the beta stimulants isoproterenol and epinephrine in asthmatics when compared with normal subjects, this decreased activity was related to severity of disease.[3,4] The beta-blocking agent propanalol has several interesting *pulmonary* effects; two of these are quite important; development of increased airway resistance following administration in the asthmatic,[5] and production of similar findings in patients with allergic rhinitis without clinical asthma following challenge with either inhaled antigen or the cholinergic stimulant, mecholyl (these agents are not usually capable of producing brochospasm when administered alone to these patients).[6,7] Two important *hematologic* observations have also been made. The eosinopenic effect of the catecholamines is lessened in the asthmatic, as well as in propanalol-blocked normal subjects, suggesting spontaneous beta blockade effect in the asthmatic.[8] Lymphocytes from patients with severe, active asthma[9] and atopic dermatitis[10] have significantly less cyclic AMP (CAMP) before and after isoproterenol stimulation than do lymphocytes from normal subjects. Cyclic AMP is a substance produced in cells by beta stimulation (see below). In some cases CAMP levels rose to normal as improvement in clinical status of asthma occurred, suggesting that beta blockade may be an acquired rather than a congenital defect.[9] Proof of this latter suggestion will require measurement of CAMP in the target organs themselves.

These concepts are also useful in understanding the effects of treatment. It is necessary, however, to first briefly review the concept of the "second messenger" proposed by Sutherland.[11,12] According to this hypothesis, a hormone (first messenger) reacts with a receptor on the target cell membrane, resulting in activation of the enzyme adenyl cyclase, which is thought to be the beta adrenergic receptor. This membrane-bound enzyme is found in all mammalian cells, except the non-nucleated red cell. It catalyzes the conversion of adenosine triphosphate (ATP) to cyclic 3′, 5′ adenosine monophosphate (CAMP), the second messenger, a nucleotide with broad biological function. CAMP is degraded by the enzyme phosphodiesterase to the inactive 5′ AMP. It has been found that several of the agents useful in treatment of asthma increase intracellular CAMP either by adenyl cyclase stimulation (for example, catecholamines) or by inhibition of phosphodiesterase (methyl xanthines for example). Accumulation of CAMP leads, in turn, to bronchial smooth muscle relaxation and inhibition of lung mast cell release of several mediators including histamine and SRS-A.[13] Szentivanyi has suggested that the abnormality common to all asthmatics may be defective airway adenyl cyclase (beta receptor) resulting in decreased amounts of the second messenger CAMP.[1] The resulting chemical disturbance produces, in turn, autonomic imbalance favoring bronchoconstriction. The basis for

other forms of atopic disease has been postulated to be localized deficiencies of adenyl cyclase in nasal tissue (allergic rhinitis) and skin (atopic dermatitis).[1]

The Irritant Cough Receptor—
"Twitchy" Lung Syndrome

Many noxious stimuli such as citric acid, charcoal and cold air inhalation result in bronchoconstriction, presumably by stimulation of subepithelial cough receptors.[14] The pathways are mediated by the vagus and can be blocked by previous administration of atropine.[14] Since asthmatic subjects have increased sensitivity to these stimuli and to inhaled allergens and many chemical mediators (such as histamine, slow reacting substance, kinins) as well as to cholinergic drugs, an increased sensitivity of the subepithelial cough-irritant receptor has been postulated by Nadel.[14] Supporting evidence of this suggestion includes prevention and reversal of both allergen and propanalol-induced bronchospasm with atropine.[15,16]

Chemical Mediators

It has been known for 30 years that histamine is not the only major mediator released from target tissue following an anaphylactic reaction. Brocklehurst, using actively and passively sensitized human tracheal tissue, showed that antihistamines could not block the smooth muscle contracting activity of a compound, now known as slow reacting substance of anaphylaxis (SRS-A), which is formed and released, after antigen stimulation, from contracting guinea pig ileum.[17] Austen and Orange, more recently, demonstrated release of histamine and SRS-A from sensitized human lung fragments following specific allergen challenge.[18] The pulmonary eosinophilic infiltrate associated with some allergic reactions and the blood eosinophilia associated with many may be the result of a newly described mediator—eosinophil chemotactic factor of anaphylaxis (ECF-A).[19] Other possibly important chemical mediators include prostaglandins, particularly the two which have been regularly shown in human lung—PGF_{2alpha} (bronchoconstrictor) and PGE_2 (bronchodilator).[20] Aerosols of PGF_{2alpha} have been shown to be eight thousand times more reactive in the asthmatic lung than in non-asthmatic controls, while histamine shows only a tenfold increase in reactivity in the same situation.[20] PGE_2 has recently been shown to be a more effective bronchodilator in guinea pigs than is isoproterenol.[21]

Release of mediators, particularly histamine and SRS-A from mast cells and basophils is modulated by the autonomic nervous system.[18] Beta-stimulating and other agents which increase intracellular CAMP levels also inhibit release of mediators after allergen-IgE union on the cell membrane. Conversely, drugs which lower intracellular CAMP levels either by beta blockade or alpha stimulation facilitate mediator release. Recently, cholinergic stimuli, probably via the mechanism of stimulation of intracellular cyclic guanosine monophosphate (C GMP) content, have been shown to enhance mediator release; this process is blocked by atropine.[22] Administration of a new pharmacological agent, disodium cromoglycate, also results in inhibition of histamine and SRS-A release, though another mechanism which causes mast cell membrane stabilization is apparently responsible.[23,24]

Immunology

Antibodies

Bronchial asthma is thought to be an example of a Type I hypersensitivity reaction (Gell and Coombs) involving combination of allergen and IgE antibodies on the surface of pulmonary mast cell.[25] This combination results in mediator release which causes bronchial smooth muscle contraction, submucosal edema and increased mucous secretion. Demonstration of mediator release from asthmatic lung tissue in vitro following challenge with appropriate allergen or with anti IgE constitutes direct evidence implicating IgE mediated reactions in the pathogenesis of asthma. Normal lung tissue also releases mediators following passive sensitization with IgE antibodies from allergic serum and challenge with specific allergen.[19] Serum IgE levels are elevated in approximately 60 percent of extrinsic (allergen-induced) asthmatics.[26]

Several studies utilizing fluorescent antibody staining for IgE as well as IgG, IgM and IgA report conflicting results. Callerame et al found a significantly higher deposition of IgG, IgM, IgA and complement (Beta 1C) along the basement membrane in asthmatics (both intrinsic and extrinsic types) than in non-asthmatic controls; the deposits in some cases resembled those found in lupus nephritis.[27] IgE was not detected in basement membrane deposits.[27] Gerber and coworkers,

however, found IgE deposits in the bronchial epithelium, basement membrane and in the bronchial glands, but not on mast cells.[28] IgE was found much less frequently in the non-asthmatic lung.[28] Other immunoglobulins and complement were not found with increased frequency in asthmatic lung tissue.[28] Problems arising out of criteria for type of asthma, drug therapy (particularly steroids), patient selection, and immunologic technique make data comparisons difficult.

Recently, mechanisms other than the classic IgE reaction for asthmatic symptoms have been emphasized and well reviewed.[25,29] In particular, a well-defined syndrome of allergic pulmonary aspergillosis comprising both airway obstruction and pulmonary infiltrates has been described; these patients show evidence of IgE (Type I) and IgG (Type III) hypersensitivity phenomena to Aspergillus fumigatus.[25,29]

Airborne allergens

Until recently it has been assumed that inhaled allergens are brought, with the inspired air, into the airways of the lung and deposited there by direct contact. It has been further thought that these allergens then dissolve in pulmonary tissue fluids and thereby produce their effects upon mast cells and bronchial musculature by local action. These seemingly obvious assumptions are, however, not in agreement with well-established aerodynamic principles concerning the behavior of particles in airstreams.[30] Materials suspended in a moving stream of air, because of their inertia, tend to continue in their original direction, even though the flow of air sharply turns to follow anatomic configurations. This inertial effect produces impaction which, combined with sedimentation, causes larger particles to adhere to the mucosa of areas of changing airflow direction such as the nasopharynx, the oropharynx and areas where airways branch.[30]

The net effect of these physical principles is that deposition of inhaled allergens in the respiratory system is determined by their size. Larger allergens, 20 to 25 micra or larger in diameter, are effectively excluded from the airways and lung, being quantitatively trapped in the nose, mouth and pharynx.[31] It is of interest that this size range includes pollens from essentially all grasses, as well as pollens from many other plants. Since grass pollen clearly causes asthma in sensitive persons, it seems likely that symptoms are produced either by absorption of antigenic material from pollen deposited in the nose, mouth or pharynx or by small fragments of pollen grains that exist freely in nature and may be inhaled deep into the lung.[31,32]

Small airborne particles such as dust (representing, at least partially, fragments of mites), some fungal spores and bits of animal skin (danders) are small enough to be deposited in the airways and lungs during inhalation.[30] It is unlikely that very large pollens, and other potentially antigenic material of similar nature will be inhaled except during very heavy exposure. Such large particles sediment very rapidly in air and therefore are airborne for very short intervals.[31]

Hyposensitization Therapy

In those cases of asthma in which inhalant allergens have been demonstrated to be clinically important, a trial of injection therapy should be attempted.[33] Postulated mechanisms[34] of action include the following:

- *Immunization.* Shortly after the institution of injection therapy, blocking IgG antibodies to the specific allergens used in therapy can be found in the serum. These antibodies prevent allergens from combining with cell-bound IgE by competitive inhibition.
- *Hyposensitization or tolerance.* After an initial rise in IgE, there is a decrease which is slow and may take years to be significantly reduced. Inhibition of IgE synthesis may be on the basis of IgG feedback,[35] or thymic derived lymphocyte (T cell) tollerance[36] which interferes with T cell-B cell interaction probably necessary for IgE antibody synthesis.
- *Change in cell sensitivity.* It has been demonstrated that following injection therapy basophils from allergic persons require increasing amounts of allergen to produce and release 50 percent of cell-bound histamine *in vitro;*[37,38] in some cases no histamine was released regardless of allergen dosage.[39] The mechanism is not clear, but a depletion of intracellular factors necessary for the allergic response may be responsible.[40]

Attempts to correlate cellular and immunological factors with clinical response have not been uniformly successful. In general, it appears that while all these factors change with injection therapy, levels of blocking antibody[41] and degree of cell sensitivity correlate best with therapeutic response.[38] Current research concerned with mechanism of IgE synthesis regulation may reveal

important methods for control of production of those IgE antibodies which result in allergic disease.

Pulmonary Pathophysiology

Site of Obstruction

Classically, the site of obstruction in asthma has been considered as occurring primarily at the bronchiolar level. However, several techniques of measurement have shown that primary source of airway resistance must occur in large airways. This concept has been supported by direct measurements of increased bronchial tone[42] and bronchographic demonstration of constriction in lobar bronchi.[43] Additionally, partitioning of airway resistance between large and small airways has shown that increased airway resistance, characteristic of asthma, is indicative of large airway obstruction.[44]

However, the original concept of obstruction at the small airway level has also been supported by certain recent findings. These include closing volume measurements[45] and the effect of various gases upon maximal expiratory flow volume curves.[46] These latter rather sophisticated measurements have demonstrated beyond doubt that small airways (2 mm in diameter or less) are frequently involved in asthma.[45,46]

The effect of bronchodilator administration may be upon either set of airways. In some cases (mainly those in which airway resistance becomes less) the effect is clearly upon larger airways. In others, mainly those in which closing volumes become less, small airways are dilated.[45] Evidence is accumulating that small airway disease may persist for variable periods even in "asymptomatic" asthma.[45,46]

In summary, it appears that both larger and smaller airways are affected by the asthmatic process and that therapy may beneficially affect either or both sets of airways.

Ventilation/Perfusion ($\dot{V}/\dot{Q}$) Abnormalities

Ventilation/perfusion relationships in asthma are somewhat complex. The manifestations of these abnormalities include hypoxemia and increased diffusing capacity.[47,48]

It has been found that areas of the lungs of many asthmatics, even when relatively asymptomatic, have abnormally decreased ventilation.[47] These abnormalities—both ventilation and perfusion—are reversible with either treatment or time. That is, one area of the lung may be involved one day and on another day a different area of the lung may be involved. The degree of regional ventilatory and perfusion abnormality correlates fairly closely with the severity of disease.

TABLE 2.—*Explanation for Arterial Hypoxemia and Hypocarbia in Asthma**

	Normal	*Asthma*
Mixed venous blood		
PO_2 mmHg	40	41
PCO_2 mmHg	46	41
O_2 content Vol. %	14.5	14.9
CO_2 content Vol. %	53.0	50.5
Arterial blood		
PO_2	95	60
PCO_2	40	36
O_2 content	19.4	18.1
CO_2 content	48.5	46.8
Blood from hypoventilated areas (31.5%)		
PO_2		41
PCO_2		41
O_2 content		14.9
CO_2 content		50.5
Blood from hyperventilated areas (68.5%)		
PO_2		101
PCO_2		33.5
O_2 content		19.6
CO_2 content		45.1

*Arterial and mixed venous blood gas data from studies on a patient with moderate asthma. For sake of simplicity it is assumed that ventilation is essentially zero in 31.5 percent of the lung but that this area is normally perfused. Note that the O_2 and CO_2 contents in arterial blood are a mixture of the gas contents of the hypoventilated and hyperventilated areas; the resulting contents of the mixture then establish the partial pressures observed in arterial blood. The small amount of ventilation/perfusion abnormality seen in the normal supine lung was ignored.

These regional $\dot{V}/\dot{Q}$ abnormalities produce a relative mismatching of ventilation to perfusion in small localized areas throughout the lung.[47] Hence, even though perfusion to an involved area is decreased, ventilation is decreased even more. This imbalance allows some blood to pass through some poorly ventilated areas and therefore not participate in gas exchange. The net effect is that CO_2 is not properly excreted from this blood nor is oxygen properly absorbed by this blood (venous admixture). As the number of these areas increases, total gas exchange is impaired further and hypoxemia becomes worse. On the other hand, arterial carbon dioxide levels (PCO_2) are not elevated, and, in fact, are decreased in asthmatic persons. This apparent paradox is due to the different shapes of the relationship between partial pressures of carbon dioxide and oxygen on the one hand and the content of chemically combined gas in the blood on the other hand (Table 2).

To appreciate the significance of these findings one must understand that the bulk of the lung is

unaffected by regional $\dot{V}/\dot{Q}$ abnormalities in the typical asthmatic patient. This relatively normal lung not only ventilates sufficiently but, apparently in response to the presence of regional abnormalities, in fact, hyperventilates.[47] Therefore, the major portion of the lung is in a state of hyperventilation whereas a small portion of the lung is suffering from the effect of venous admixture. Now, referring to Table 2, one notes that effect of hyperventilation upon carbon dioxide is to lower both the partial pressure of carbon dioxide and the content of carbon dioxide in the blood. The net result of mixing large areas of hyperventilation with small areas of venous admixture results in a situation where hyperventilation predominates and, therefore, arterial PCO_2 is lower. On the other hand, hyperventilation increases the partial pressure of oxygen but does not increase significantly the content of oxygen in the blood. Therefore, arterial PO_2 is decreased since blood which comes from hyperventilated areas of the lung cannot compensate for the low oxygen content of venous admixture blood. Hence, the combined blood will always be lower than normal in oxygen content, and partial pressure of oxygen (PO_2) will be decreased (Table 2).

This type of ventilation/perfusion mismatching is not limited to asthma but may be seen in several other diseases of the lung including bronchitis, pneumonia and pulmonary fibrosis; it is not observed in pure emphysema.[49]

Mechanisms underlying these regional $\dot{V}/\dot{Q}$ abnormalities are not clear. Possible causes include obstruction due to localized brochospasm, local collection of airway mucous, and chance deposition of allergens in particular airways (see above). What causes the perfusion abnormalities is even more obscure. It has been suggested that the regional blood flow abnormalities may be due to local hypoxia, or to increased alveolar pressure, or to local release of vasospasm-causing mediators, or to combinations of these factors. There is evidence that both hypoxemia and vasospastic agents may play roles.[50] The presence of vasospasm is probably beneficial since shunting some of the blood away from the poorly ventilated areas reduces venous admixture and the consequent hypoxemia. Inhaled bronchodilators may cause increased hypoxemia apparently because they are preferentially directed to already well ventilated areas and may increase perfusion generally, thereby increasing relative blood flow to poorly ventilated areas.[51]

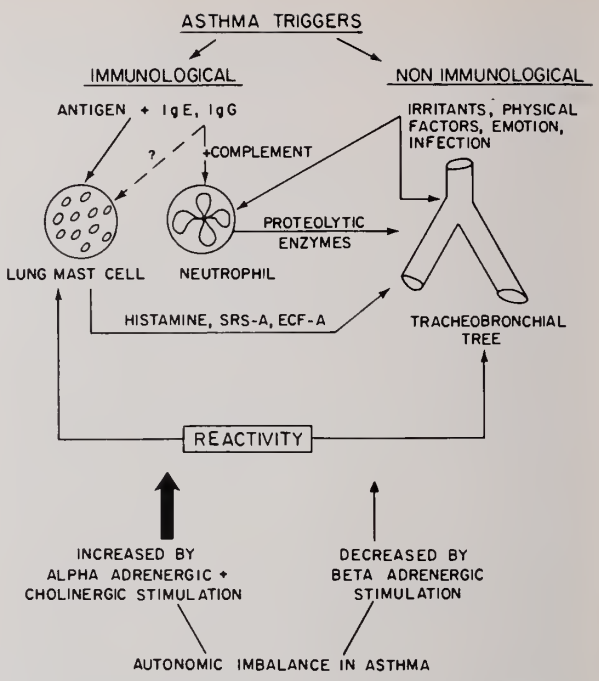


Chart 1.—In bronchial asthma, airway obstruction appears to be the result of non-specific noxious stimuli or immunologic phenomena or both. An attractive hypothesis is that the basic abnormality is an imbalance between factors responsible for relaxation of bronchial smooth muscle and those controlling stability of mast cells. Mediator release may be controlled through maintenance of adequate CAMP levels in these tissues. Agents which lower CAMP or stimulate cholinergic receptors (resulting in elevated intracellular C GMP levels), facilitate bronchial smooth muscle contraction and mediator release.

Single breath diffusing capacity for carbon monoxide (D_LCO) is dependent upon several factors: Reasonable distribution of inspired gas to the alveoli; the presence of blood flow to these alveoli; and a normal membrane between the gas and blood phases. As we have seen in the preceding section, distribution of both ventilation and perfusion are abnormal in asthma; therefore, we might expect *a priori* that D_LCO would be reduced in asthma. However, in fact, D_LCO tends to be increased in asthma about 15 percent more than normal.[48] This paradox can be shown to be due to increased blood flow to the uppermost (apical) regions of the upright lung.[48] This increased blood flow to the upper lung is probably due to increased pulmonary artery pressure.[52] The cause of this probably increased pulmonary artery pressure has not been established. Possible causes include pulmonary vasospasm and increased cardiac output; available evidence favors the former.[48]

The net effect of increased apical blood flow is reduction of the normal high $\dot{V}/\dot{Q}$ relationship pertaining to the upper lung; hence $\dot{V}/\dot{Q}$ matching is more uniform and D_LCO is increased in the apical portions of the lung. Though the presence of low $\dot{V}/\dot{Q}$ areas throughout the lung will reduce D_LCO, increased apical blood flow more than compensates for these low $\dot{V}/\dot{Q}$ areas.[48]

Pulmonary Parenchymal Changes

In the section above, it was noted that asthma may affect the function of the airways and pulmonary blood vessels even during the so-called "asymptomatic" period. It is tacitly assumed that these reactive structures constrict under the influence of chemical mediators, proteolytic enzymes and other pathophysiological stimuli (Chart 1). While the physical interpretation of these reactions is not puzzling, concomitant changes in the pulmonary parenchyma are somewhat surprising.

Lung tissue resistance, though only slightly higher than normal in asthmatic subjects, increased four-fold during provocation of an asthmatic attack by histamine inhalation; simulation of an asthmatic attack by breathing through external resistances did not increase lung tissue resistance.[53] Decreased elastic recoil of the lungs has been demonstrated both during naturally-occurring airway obstruction and for up to two weeks following relief of obstruction by treatment. These changes could not be duplicated by either histamine inhalation or extrathoracic negative pressure.[54] Since the decreased elastic recoil was reversible with time or treatment, it was not due to a destructive process like emphysema. The differing pulmonary parenchymal changes associated with asthma—slightly increased lung tissue resistance increasing after histamine[53] and decreased elastic recoil not changing with histamine[54]—are puzzling and fascinating; these findings need confirmation and simultaneous measurement in the same group of patients.

REFERENCES

1. Szentivanyi A: The beta adrenergic theory of the atopic abnormality in bronchial asthma. J Allergy 42:203-232, 1968

2. Lands AM, Arnold A, McAuliff JP, et al: Differentiation of receptor system activated by sympathomimetic amines. Nature 214: 597-598, 1967

3. Lockey SD Jr, Glenn JA, Reed CE: Comparison of some metabolic responses in normal and asthmatic subjects to epinephrine and glucagon. J Allergy 40:349-354, 1967

4. Inone S: Effects of epinephrine on asthmatic children. J Allergy 40:335-338, 1967

5. McNeill RS: Effect of a beta-adrenergic blocking agent, propanolol, on asthmatics. Lancet 2:1101-1102, 1964

6. Oullette JJ, Reed CE: The effect of partial beta adrenergic blockade on the bronchial response of hay fever subjects to ragweed aerosol. J Allergy 39:160-166, 1967

7. McNeill RS, Ingram CG: Effect of propanolol on ventilatory function. Am J Cardio 18:473-475, 1966

8. Reed CE, Cohen M, Enta T: Reduced effect of epinephrine on circulating eosinophils in asthma and after beta adrenergic blockade or Bordetella pertussis vaccine. J Allergy 46:90-102, 1970

9. Parker CW, Smith JW: Alterations in cyclic adenosine monophosphate metabolism in human bronchial asthma. J Clin Invest 52:48-59, 1973

10. Parker CS, Eisen AZ: Altered cyclic AMP metabolism in atopic eczema. Clin Res 20:418, 1972

11. Robison GA, Butcher RW, Sutherland EW: Adenyl cyclase as an adrenergic receptor. Ann New York Acad Sci 139:703-723, 1967

12. Sutherland EW, Robison GA: The role of cyclic 3′, 5′ AMP in responses to catecholamines and other hormones. Pharmacol Rev 18:145-161, 1966

13. Middleton E Jr: Autonomic balance in asthma with special reference to beta adrenergic blockade. Adv Int Med 19:177-197, 1973

14. Simonsson BG, Jacobs FM, Nadel JA: Role of autonomic nervous system and the cough reflex in the increased responsiveness of airways in patients with obstructive airway disease. J Clin Invest 46:1812-1818, 1967

15. Ju DYC, Galant SP, Gold WM: The role of the parasympathetic nervous system in human asthma: Inhibition of antigen-induced bronchoconstriction by atropine in asthmatic patients. J Appl Physiol 32:823-828, 1972

16. Grieco MH, Pierson RN, Jr: Mechanism of bronchoconstriction due to beta adrenergic blockade, studies with practolol, propanolol and atropine. J Allergy Clin Immunol 48:143-152, 1971

17. Brocklehurst WE: The release of histamine and formation of a slow-reacting substance (SRS-A) during anaphylactic shock. J Physiol 151:416-435, 1960

18. Orange RP, Austen GW, Austen KF: The immunological release of histamine and slow-reacting substance of anaphylaxis from human lung—1. Modulation by agents influencing cellular levels of cyclic 3′, 5′ adenosine monophosphate. J Exper Med (Supp.) 134:136-148, 1971

19. Kay AB, Austen KF: The IgE mediated release of an eosinophil leukocyte chemotactic factor from human lung. J Immunology 107:899-902, 1971

20. Parker C: Prostaglandins and asthma. Annals Int Med 78: 963-964, 1973

21. Adolfson RL, Townley RG: A comparison of bronchodilator activities of isoproterenol and prostglandin E_1 aerosols. Chest 63: 5-6, 1973

22. Kaliner M, Orange RP, Austen KF: Immunological release of histamine and slow reacting substance of anaphylaxis from human lung—IV. Enhancement of cholinergic and alpha adrenergic stimulation. J Exp Med 136:556-567, 1972

23. Pepys J, Hargreave FE, Chan M, McCarthy DS: Inhibitory effects of disodium cromoglycate (Intal) on allergen inhalation tests. Lancet II:134-137, 1968

24. Assem ESK, Richter AW: Comparison of in vivo and in vitro inhibition of anaphylactic mechanism by beta adrenergic stimulants and disodium cromoglycate. Immunol 21:729-739, 1971

25. McCombs R: Diseases due to immunologic reactions in the lungs. N Engl J Med 286:1186-1194, 1972

26. Johansson SGO: Raised levels of a new immunoglobulin class (IgND) in asthma. Lancet 2:951-953, 1967

27. Callerame ML, Condemi JJ, Ishizaka K, et al: Immunoglobulins in bronchial tissues from patients with asthma, with special reference to immunoglobulin E. J Allergy 47:187-197, 1971

28. Gerber MA, Paronetto F, Kochwa S: Immunohistochemical localization of IgE in asthmatic lungs. Am J Path 62:339-348, 1971

29. Pepys J: Immunopathology of allergic lung disease. Clin Allergy 3:1-22, 1973

30. Cadle R: Particle Size: Theory and Industrial Applications. New York, Reinhold Publishing Corp, 1965

31. Wilson AF, Novey HS, Berke RA, et al: Deposition of inhaled pollen and pollen extract in human airways. N Engl J Med 288:1056-1058, 1973

32. Busse WW, Reed CE, Hoehne JH: Where is the allergic reaction in ragweed pollen?—11. Demonstration of ragweed antigen in airborne particles smaller than pollen. J Allergy Clin Immunol 50:289-293, 1972

33. Johnstone DE, Dutton A: The value of hyposensitization therapy for bronchial asthma in children—A 14 year study. Ped 42:793, 1968

34. Ellis E: Immunologic basis of atopic disease. Adv Ped 16: 65-98, 1969

35. Tada T, Okumura K: Regulation of homocytotropic antibody formation in the rat—1. Feedback regulation by passively administered antibody. J Immunol 196:1002-1011, 1971

36. Roitt I: Essential immunology. London, Blackwell Scientific Publication, 1971, p 111

37. Levy DA, Lichtenstein LM, Goldstein EO, et al: Immu-

nologic and cellular changes accompanying the therapy of pollen allergy. J Clin Invest 50:360-369, 1970

38. Pruzansky SL, Patterson R: Histamine release from leukocytes of hypersensitive individuals—II. Reduced sensitivity of leukocytes after injection therapy. J Allergy 39:44-50, 1967

39. Sadan N, Rhyne MB, Mellits ED, et al: Immunotherapy of pollinosis in children—Investigation of the immunologic basis of clinical improvement. N Engl J Med 280:623-627, 1969

40. Lichtenstein LM, Levy DA: Is 'Desenitization' for ragweed hayfever immunologically specific? Int Arch Allergy 42:615-626, 1972

41. Lichtenstein LM, Norman PS, Winkenwender WL: A single year of immunotherapy for ragweed hayfever. Annals Int Med 75: 663-671, 1971

42. Douglas A, Simpson D, Merchant S, et al: The measurement of endomural bronchial (or "squeeze") pressures in bronchitis and asthma. Am Rev Resp Dis 93:693-702, 1966

43. Gayrard P: The role of the main bronchi in the asthmatic attack. Rev Franc Allerg 8:34-49, 1968

44. Hogg JC, Macklem PT, Thurlbeck WM: Site and nature of airway obstruction in chronic obstructive lung disease. N Engl J Med 278:1355-1360, 1968

45. McCarthy D, Milic-Emili J: Closing volume in asymptomatic asthma. Am Rev Resp Dis 107:559-569, 1973

46. Despas PJ, Leroux M, Macklem PT: Site of airway obstruction in asthma as determined by measuring maximal expiratory flow breathing air and a helium-oxygen mixture. J Clin Invest 51: 3235-3243, 1972

47. Wilson AF, Surprenant EL, Beall GN, et al: The significance of regional pulmonary function changes in bronchial asthma. Am J Med 48:416-423, 1970

48. Weitzman R, Wilson AF: Diffusing capacity and overall ventilation-perfusion in asthma. Am J Med (In press)

49. Surprenant EL, Wilson AF, Bennett LR: Clinical application of regional pulmonary function studies. Radiology 99:623-631, 1971

50. Wilson AF, Surprenant EL, Novey HS: Unpublished results

51. Chick TW: Effects of isoproterenol on distribution of ventilation and perfusion in asthma. Am Rev Resp Dis 107:869-873, 1973

52. Helander E, Lindell SE, Soderholm B, et al: The pulmonary circulation and ventilation in bronchial asthma. Acta Allerlog 21: 441-465, 1966

53. Bachofen H: Lung tissue resistance in normal and asthmatic subjects. Helv Med Acta 33:108-121, 1966

54. Gold WM, Kaufman HS, Nadel JA: Elastic recoil of the lungs in chronic asthmatic patients before and after therapy. J Appl Physiol 23:433-438, 1967

Medical Staff Conference

Refer to: Immunoglobulin deficiency disorders—Medical Staff Conference, University of California, San Francisco. West J Med 120:471-475, Jun 1974

Immunoglobulin Deficiency Disorders

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *In the past few years there have been major advances in our knowledge about the mechanisms by which we are defended from the invasion of microorganisms and perhaps from malignant transformations as well. These advances come from the work of immunologists, biochemists and cell physiologists and have been rapidly applied in clinical investigations. Unfortunately the host defense mechanisms may go awry. Today we shall discuss a patient with a particular form of immungolubin deficiency complicated by recurrent infections, iatrogenic hepatitis and renal disease of unknown cause. Dr. Lee Goldman will present the case summary.*

DR. GOLDMAN:† The patient is a 36-year-old Mexican-American mechanic who has had common variable hypogammaglobulinemia since 1968. At the age of 29 he had recurrent bacterial pneumonia and pyoderma due to Staphylococcus aureus. In 1967 he was noted to have generalized lymphadenopathy and hepatosplenomegaly with elevated bromsulphalein (BSP) retention and serum alkaline phosphatase. A liver biopsy showed chronic inflammation with possible granulomas. Serum immunoglobulins were: IgG 260 mg per 100 ml, IgA 0 and IgM 15 mg per 100 ml. Pulmonary function tests showed restrictive disease; numerous areas of scarring and bronchiectasis were seen on chest roentgenograms. Bone marrow aspirate showed absence of plasma cells. The patient was treated with intramuscular gamma globulin and intermittent plasma infusions.

In 1968 staphylococcal pyoderma was followed by sepsis and infection of his right kidney which led to a nephrectomy. The postoperative course was complicated by a persistent S. aureus wound infection.

In 1969 following a plasma infusion the patient had hepatitis B antigen (HbAg) positive hepatitis with very slow resolution of hepatic inflammation. In 1971, due to progressive splenomegaly and pancytopenia, splenectomy was performed. In 1972 an exacerbation of hepatitis followed postoperative blood transfusions and resolved slowly.

In 1973 the patient experienced an allergic reaction to cholangiographic dye, and a hypotensive episode following accidental intravenous injection of gamma globulin.

The present admission in 1974 was for bacterial pneumonia with hydropneumothorax and

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine.

†Lee Goldman, MD, Intern in Medicine.

deteriorating renal function. The creatinine clearance on his present admission was 40 ml per minute, and urinalysis showed moderate proteinuria.

Dr. Stites:* This patient illustrates many of the problems in the diagnosis and management of patients with immunologic deficiency disorders. His specific disease entity is termed common variable hypogammaglobulinemia (CVH), which was previously called adult-acquired agammaglobulinemia. The patient's childhood was relatively free of infection. The onset of his disease occurred in the third decade of life with recurrent pyogenic infections. His disorder was initially diagnosed in another hospital as sarcoid because of chronic lung disease and hepatic granulomatosus. However, review of the biopsies of his liver did not show granulomas but areas of chronic inflammation in portal triads. His infection history over the course of his disease has been very characteristic of a patient with a humoral immune deficiency disorder. That is to say, his problem is mainly with Gram-positive pyogenic organisms, especially staphylococcus, and only occasionally with Gram-negative coliform bacteria. This is in contrast to cellular immune deficiency, in which fungal infections, pneumocystis, viruses, or other opportunists present problems. In 1969 this patient had a catastrophic infection following pyoderma. Twenty-four hours after a boil on his hand developed, hematogenous spread of Staphylococcus aureus ensued and actually liquefied his right kidney. This patient has another prominent manifestation of a humoral immune deficiency disorder—chronic lymphoid hyperplasia. This abnormality often has been confused clinically, and at times histopathologically, with malignant lymphoma. The patient in the present case had a very large spleen, an enlarged liver, and generalized lymphadenopathy. However, biopsies of these tissues have never shown any cells suggestive of malignant change, and the only serious clinical consequence was pancytopenia three years ago which responded very well to splenectomy.

At the time of the renal infection, a lymph node biopsy taken from a mesenteric node illustrated the histopathologic changes one finds in a patient with B cell or plasma cell deficiency. There was a fairly monotonous appearance of lymphocytes spread throughout the stroma, which contained some increase in fibrous tissue. Of great importance was the absence of follicles and germinal centers, the areas in which antibodies are produced. The patient has had iatrogenic diseases as well, particularly HbAg-positive hepatitis which occurred following the administration of a contaminated unit of plasma which was being given for replacement therapy. He had had one very serious anaphylactoid, probably non-allergic, reaction to an accidental intravenous injection of aggregates of gamma globulin. These reactions to aggregates result from the activation of the complement system with release of histamine, a process similar to that which occurs in immune complex disease. All of us should be certain when giving patients gamma globulin for hepatitis prophylaxis, or for any other reason, that the gamma globulin is not administered intravenously.

The final clinical point, which is the most puzzling and probably the most important to the patient at this point, is the necessity of determining the nature of the pathologic process in his remaining kidney. One suspects that he probably has chronic glomerulonephritis but of unknown cause. Amyloidosis has been ruled out by appropriate stains on tissues taken from previous surgical specimens.

Now I would like to turn to a general discussion of humoral immune deficiency disorders. It is convenient to divide all those humoral immune deficiencies involving immunoglobulins into two major categories: so-called primary immunodeficiencies, which are really idiopathic diseases (Table 1), and secondary immunologic deficiency

TABLE I.—*Immunoglobulin Deficiency Disorders*

Primary Panhypogammaglobulinemias
1. Transient hypogammaglobulinemia of infancy
2. X-linked hypogammaglobulinemia (Bruton's)
3. Common variable hypogammaglobulinemia
4. Severe combined immunodeficiency (Swiss type)

Selective Immunoglobulin Deficiencies
1. Wiscott-Aldrich syndrome—IgM
2. Ataxia telangiectasia—IgA+IgE
3. Dysgammaglobulinemias—IgA

Secondary Hypogammaglobulinemia
1. Lymphoreticular malignancies
   a. Myeloma
   b. Macroglobulinemia
   c. Lymphoma
   d. Chronic lymphocytic leukemia
2. Rheumatoid diseases
3. Neoplasia
4. Protein-losing diseases
   a. Nephrosis
   b. Uremia
   c. Protein-losing enteropathy
5. Diabetes mellitus

*Daniel Stites, MD, Assistant Professor of Medicine.

disorders which are commonly seen by hematologists and oncologists in patients in whom the depression of serum gamma globulin levels is the result of an underlying disease process or the treatment of it.

There are four types of primary panhypogammaglobulinemia involving all classes of immunoglobulins (IgG, IgA, IgM, IgD and IgE). The first is a relatively benign condition seen by pediatricians—transient hypogammaglobulinemia of infancy. Babies are born with predominantly maternal gamma globulin, and as it naturally decays during the first six months of life the infant's own immunoglobulin system becomes competent. Some children have a prolonged physiologic depression of initiation of gamma globulin synthesis; it may last as long as two or three years. These children all have excellent prognosis and rarely require treatment. The importance of recognizing this disorder is to differentiate it from the more serious genetic diseases with poorer prognosis and which require life-long gamma globulin replacement therapy.

The first inherited immunoglobulin deficiency disorder was recognized by Colonel Ogden Bruton in 1952.[1] It is now called X-linked hypogammaglobulinemia. This is a pure B cell or plasma cell deficiency in which normal cellular immunity is present but with very low concentrations of circulating immunoglobulins.

The disease in the patient we are discussing today, common variable hypogammaglobulinemia, is probably the most common of these three genetic diseases (Table 1).

The fourth type of hypogammaglobulinemia, so-called Swiss type hypogammaglobulinemia, is now called severe combined immuno-deficiency disorder—using the new WHO terminology.[2] This is a disease involving deficiencies of both B cells and T cells but has two different genetic forms of inheritance, an autosomal recessive and an X-linked recessive pattern. It involves severe deficiency in both humoral and cellular immunity, and unless there is some kind of cellular replacement therapy directed at improving the patient's immune status it is usually fatal within the first year or two of life. This disease has been treated successfully with bone marrow transplantation.

There also exists a series of diseases which involve selective lesions in various immunoglobulin classes. Some of the better known are the Wiscott-Aldrich syndrome, which involves cellular immune deficiency and a deficiency of IgM; and ataxia telangiectasia, a complicated neuro-immunologic disorder with a depression of cellular immunity, a very high incidence of lymphoreticular malignant disease, cerebellar ataxia, telangiectasia and IgA and E deficiencies. The term *dysgammaglobulinemia* refers to a depression of one but not all of the immunoglobulin classes. IgA deficiency is the most common of these—actually the most common humoral immune deficiency of all, occurring in about 1 in 600 of the "normal" population. The incidence of tumors, autoimmune diseases, chronic sinopulmonary infections, and chronic inflammatory diseases of the gastrointestinal tract is much higher in IgA deficiency than in the normal population.[3] One of the most important aspects of IgA deficiency was the recognition by Dr. Vyas and Dr. Fudenberg a few years ago[4] that when patients who have no IgA in their serum receive blood transfusions, fatal anaphylactoid reactions can result, due to the fact that the IgA in the transfused blood is recognized as a foreign protein. Thus, the diagnosis of this disorder is of more than just an academic interest, and patients who have IgA deficiency and need blood or plasma products need to be given IgA deficient plasma or blood to avoid these reactions.

The secondary hypogammaglobulinemic disorders are much more common than the primary ones. In most there is hypercatabolism or loss of gamma globulin, whereas in the primary disorders failure of synthesis is the underlying pathogenesis.

When should a physician seeing a patient with recurrent infections suspect that the patient might have hypogammaglobulinemia, and what can one do to make the diagnosis? In Table 2 is a useful list of the presenting problems of 176 patients with hypogammaglobulinemia collected in a British Medical Research Council trial.[5] The most common problem, present in 87.6 percent of these patients, was sinopulmonary infections. Diarrhea was also seen rather frequently, and other infections and problems appeared with lower frequencies. It is basically the patient who presents in the second or third decade of life with recurrent staphylococcal infections or serious bacterial pneumonias who needs to be examined immunologically for the presence of hypogammaglobulinemia.

How does one make the diagnosis? In the laboratory a battery of tests is available, and a list of the more useful ones is presented in Table 3. Serum protein electrophoresis is a readily available laboratory procedure useful in screening for

TABLE 2.—*Main Presenting Symptoms of Patients Admitted to the British Medical Research Council Trial*[5]

Presenting symptoms	*Total No.*	*Percent*
Respiratory infections	153	
respiratory tract infection only	69	
with meningitis or septicemia	17	
with gastrointestinal tract infection	22	87.6
with skin or eye infections	18	
with infections of several systems	27	
Diarrhea only	3	1.7
Urinary infection only	1	0.6
Skin infection only	2	1.2
Tuberculosis	3	1.7
Generalized vaccinia	1	0.6
Rubella syndrome	1	0.6
Blood disease	2	1.2
Failure to thrive	4	2.3
No presenting symptoms but family history of hypogammaglobulinemia	6	3.5
TOTAL	176	100.0

TABLE 3.—*Laboratory Diagnosis of Immunoglobulin Deficiencies*

1. Serum protein electrophoresis
2. Immunoelectrophoresis
3. Radial immunodiffusion
4. Bone marrow examination
5. Lymph node biopsy
6. Exclude secondary causes
   - Renal-proteinuria
   - Gastrointestinal—stool loss
   - Neoplasm
   - Lymphoreticular malignancy
7. Special B cell and T cell assays

hypogammaglobulinemia. Immunoelectrophoresis is only a semi-quantitative assay but is particularly helpful for identifying patients with selective deficiencies of one of the major immunoglobulin classes. Radial immuno-diffusion is a quantitative assay which permits precise evaluation and diagnosis of immungoglobulin deficiency states. Bone marrow examination and lymph node biopsy are not absolutely necessary, but when they are available they help to establish the cellular defect responsible for the particular immune deficiency disorder in question. Certainly one should attempt to exclude secondary causes for immunoglobulin deficiencies, especially since these diseases require specific forms of therapy. Special T and B cell functional assays are currently in the developmental stage.

Cell mediated immunity in patients with common variable hypogammaglobulinemia (CVH) is variable. Some patients have normal cellular immunity; but as the disease progresses, cellular immunity seems to decrease, and this may be associated with an increased incidence of tumors in later life. As judged by skin tests alone, about half of our patients do have detectable delayed hypersensitivity.[6]

The survival of immunoglobulins is altered in CVH. IgG has a 21-day half-life in normal persons. Patients with common variable hypogammaglobulinemia actually have a prolonged survival of their own small amounts of IgG as well as a prolonged survival of passively administered IgG. The survival of IgG is 70 to 80 days in such patients, whereas in the patient with protein-losing enteropathy or secondary hypogammaglobulinemia who is exuding enormous quantities of all kinds of serum proteins into the gut, IgG has a shortened survival.

In the 1960s the Medical Research Council in England designed a trial to attempt to determine the effective dose of intramuscular gamma globulin for these patients, and I should like to summarize some of the many important clinical findings in this interesting population of patients.[5] One hundred seventy-six patients with serum IgG of less than 600 mg per 100 ml were included in this study. Hypogammaglobulinemia in Britain is a rare disease; only 15 per million males and 4 per millon females in England have the disease. The cause of death in the 40 of 176 patients who died during the trial was mostly due to infection; however, 10 percent died from malignant disease and 10 percent from vaccinia, which was an iatrogenic disease caused by accidental vaccination of patients who had combined humoral and cellular immune deficiency disorders. Hematological problems occurred in 20 percent of patients. Megaloblastic anemia was very common but was not due to folate or vitamin B-12 deficiencies. Neutropenia and thrombocytopenia were usually associated with hypersplenism, and lymphoreticular hyperplasia and a Coombs-negative hemolytic anemia occurred in some of the patients. Many of these patients had chronic diarrhea which was very often associated with Giardiasis and malabsorption. Hepatitis usually occurred as an iatrogenic disease, and nodular lymphoid hyperplasia of the small bowel, which is an unusual but very dramatic disease, occurred in some patients. Patients with hypogammaglobulinemia can have "auto-immune" diseases such as polyarthritis, lupus, dermatomyositis, and Sjögren's syndrome. There is a sero-negative rheumatoid-like arthritis that occurs in patients with this disorder, and it is improved by the administration of gamma globulin. Neoplasms in general are probably about

TABLE 4.—*Malignancy Disease Incidence in Primary Immunodeficiencies*

	Incidence	*Percent*
X-linked hypogammaglobulinemia	6 of 100	6
Severe combined immunodeficiency	9 of 400	2
IgM deficiency	6 of 70	8
Wiscott-Aldrich syndrome	24 of 300	8
Ataxia telangiectasia	52 of 500	10
Common variable hypogammaglobulinemia	41 of 500	8
TOTAL	138 of 1870	7

ten times more common in this series of patients than they are in normal persons. Table 4 shows the incidence of malignant disease in immune deficient patients recently reported by Kersey et al.[7] Amyloidosis has been reported in four patients, and sarcoid has been present in some hypogammaglobulinemic patients.

Can patients with hypogammaglobulinemia have allergic reactions? One might think not, since IgE levels are greatly reduced.[8] However, well documented allergic reactions can occur in patients with undetectable IgE, and I do not understand why, except to say that there obviously are other means of setting off the series of reactions we call allergic response.

A number of years ago Douglas and Fudenberg[9] showed that when peripheral blood lymphocytes from CVH patients were stimulated with phytohemagglutinin, depressed responses resulted. A formal genetic analysis of the lymphocyte responses in a large number of relatives of affected patients suggested that it is a genetic, but noncongenital disorder which expresses itself in later life.

I would like to conclude with some comments on the therapy of hypogammaglobulinemia. Antibiotics are obviously of great importance. We do not believe in continuous prophylactic antibiotic therapy, though some of our patients do, and regardless of what we tell them, they take antibiotics continuously. The rapid diagnosis and therapy of specific infections are extremely important as in any patient with depressed host defense mechanisms. Our standard form of replacement therapy is intramuscular gamma globulin (approximately 20 ml) every three weeks. This gamma globulin is absorbed slowly from the intramuscular repository site; most of it gets into the serum within a week or two after injection, and then it is slowly degraded over a period of 60 to 70 days. With this therapy the incidence of serious bacterial infections has been greatly reduced. We would like to think that there are better ways of giving gamma globulin, and if we solve the aggregate problem, intravenous gamma globulin would be of great advantage since we could administer larger volumes. Plasma infusions, which were popularized mainly by Stiehm and Fudenberg[10] here a number of years ago, definitely play a role in boosting immunity in these patients. One therapy gives IgA possibly nonspecific factors and some of those patients have mild depression of their complement activity. However, this mode of therapy carries with it the risk of hepatitis which fortunately we can now minimize somewhat by HbAg screening of the plasma to be administered.

REFERENCES

1. Bruton OC: Agammaglobulinemia. Pediatrics 9:722-727, Jun 1952
2. Fudenberg HH, Good RA, Goodman HC: Primary immunodeficiencies. Pediatrics 47:927-946, May 1971
3. Ammann AJ, Hong R: Selective IgA deficiency: Presentation of 30 cases and a review of the literature. Medicine 50:223-236, May 1971
4. Vyas GN, Perkins HA, Fudenberg HH: Anaphylactoid transfusion reactions associated with anti-IgA. Lancet 2:312-315, Aug 1968
5. Hypogammaglobulinemia in the United Kingdom, H. M. Stationery Office, London, 1971, MRC Special Report Series No. 310
6. Douglas SD, Goldberg LS, Fudenberg HH: Clinical, serologic and leukocyte function studies on patients with idiopathic "acquired" agammaglobulinemia and their families. Am J Med 48:48-53, Jan 1970
7. Kersey JH, Spector BD, Good RA: Primary immunodeficiency diseases and cancer: The Immunodeficiency Cancer Registry. Int J Cancer 12:333-347, Jun 1973
8. Stites DP, Ishizaka K, Fudenberg HH: Serum IgE concentrations in hypogammaglobulinemia and selective IgA deficiency studies on patients and family members. Clin Exp Immunol 10:391-397, Mar 1972
9. Douglas SD, Kamin RM, Fudenberg HH: Human lymphocyte response to phytomitogens in vitro: Normal, agammaglobulinemic and paraproteinemic individuals. J Immun 103:1185-1195, Dec 1969
10. Stiehm ER, Vaerman JP, Fudenberg HH: Plasma infusions in immunologic deficiency states: Metabolic and therapeutic studies. Blood 28:918-935, Dec 1966

Important Advances in Clinical Medicine

Epitomes of Progress—Neurology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in Neurology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in Neurology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities
California Medical Association, 731 Market St., San Francisco, CA 94103

"Cerebellar Pacemakers"

THE MAJORITY of patients with convulsive disorders are well controlled by the daily administration of anticonvulsant medications. There is, however, a small group of patients who are not controlled regardless of drug type, dosage, or number of drugs used. Patients in this category are usually considered for some surgical procedure to improve convulsive control, particularly if there is evidence of a progressive neurological deficit.

The goal of any surgical procedure in such cases is to remove the epileptogenic focus, and criteria for patient selection have included clinical focal abnormality, radiographic evidence of cerebral lesion and a focal abnormality on the electroencephalogram (EEG). That EEG focus may be better shown by using nasopharyngeal or sphenoidal leads or both, electrocorticography, and depth electrodes.

Surgical procedures have included the excision of the cortical epileptogenic focus, temporal lobectomy for temporal lobe (psychomotor) epilepsy, hemispherectomy, surgical disconnection of cerebral hemispheres, and stereotaxic amygdalotomy. More recently, Cooper et al have implanted electrodes on the cerebellum of patients with intractable epilepsy and applied a continuously modulated low voltage, low frequency stimulation with a remarkable improvement in convulsive control. There has been no long term observation of patients treated with this "cerebellar pacemaker," however.

Of those patients carefully studied and selected for surgical treatment of intractable convulsions, one-third to one-half are fit-free or nearly fit-free following operation. These patients continue to require anti-convulsive drugs, despite this improvement.

BRUCE O. BERG, MD

REFERENCES

Falconer M, Taylor D: Surgical treatment of drug-resistant epilepsy due to medial temporal sclerosis. Arch Neurol 19:353-361, Oct 1968

Narabayashi H, Mizutani T: Epileptic seizures and the stereotoxic amygdalotomy. Confin Neurol 32:289-297, 1970

Jasper H, Ward A, Pope A: Basic Mechanisms of the Epilepsies. Boston, Little Brown & Co, 1969

Luessensop A, dela Cruz T, Fenichel G: Surgical disconnection of the cerebral hemispheres for intractable seizures. JAMA 213: 1630-1636, Sep 7, 1970

Migraine: The Pill and Pregnancy

ORAL CONTRACEPTIVES (OC) are variously thought to cause migraine, cure it or cause stroke in migraineurs. Confusion may derive from (1) coincidences due to the frequency of migraine (10 to 19 percent) and OC use (10 to 25 percent) among women in childbearing years; (2) failure to determine who had migraine before taking the pill; (3) imprecision in the diagnosis of migraine; (4) failure to distinguish between types of migraine and (5) the many different types of OC studied.

Migraine is very sensitive to hormonal changes with menarche, menses, pregnancy and menopause. "Classical" migraine (visual scotoma or scintillation) may be aggravated by pregnancy. "Common" migraine, preceded by irritability and associated with unilateral throbbing pain and vomiting, is often relieved by pregnancy. Unfortunately, most reports do not separate common from classical migraine.

Migraine develops for the first time in 4 to 17 percent of pregnant women. Pre-existing migraine is unchanged or becomes worse in 11 to 23 percent of pregnancies and improves in 80 percent. About 10 to 11 percent of women develop significant new headache when using OC. Headache may be less frequent and contraception less effective with preparations that are pure or predominantly progestin. Of those women starting use of OC for contraception who have pre-existing migraine, about 36 percent have fewer or no headaches, 18 percent have more and 46 percent are unchanged. OC or progestins used to treat migraine are no better than placebos, or only slightly so, and have significant side effects.

Pre-existing migraine has been considered a relative contraindication to use of OC in the face of inadequate data. Since stroke infrequently complicates migraines characterized by contralateral sensory or motor prodrome, and since stroke is a known complication of OC use, the combination is worrisome.

Either vascular headache developing *de novo* in women taking OC or an increase in frequency or severity of migraine accompanying use of OC may be an indication for discontinuation of OC, especially if accompanied by focal neurological symptoms. These changes with the use of OC may identify young women abnormally prone to stroke. Even mild hypertension is a strong relative contraindication to "the pill," because hypertension may aggravate previous migraine, because hypertension may identify women who are more prone to stroke when using OC and because OC themselves may cause hypertension.

ROBERT I. PFEFFER, MD
STANLEY VAN DEN NOORT, MD

REFERENCES

Graham JR: Seven common headache profiles. Neurol 13:16-23, 1963

Larsson-Cohn U, Lundberg PO: Headache and treatment with oral contraceptives. Acta Neurol Scand 46:267-278, 1970

Gardner JH, Horenstein S, van den Noort S: The clinical characteristics of headache during impending cerebral infarction in women taking oral contraceptives. Headache 8:108-111, 1968

Kjaer M, de Fine Olivarius B, Waarst A: Cerebral ischemic lesions and oral contraception. Dan Med Bull 18:129-137, 1971

The Pill and Stroke

FEW MEDICAL ISSUES have evoked more furor in the profession, the pharmaceutical industry or the nation than the relation of oral contraceptives (OC) to stroke. Early reports, neglecting the occurence of stroke in women not using "the pill" had no population-base or control data. (A curious omission in considering the complications of contraceptives in non-pregnant young women was the lack of comparison with pregnancy.) Stroke unquestionably but uncommonly occurs in both men and women under 45 years old probably one-fourth to one-eighth as often as in the next two decades of life. One-tenth to one-third of the women so afflicted are pregnant or puerpural; many of the remainder have predisposing causes such as diabetes, hypertension, collagen disease or aneurysm.

Retrospective British studies in 1968 and 1969 showed a 6-fold to 8-fold increase in risk of hospitalization or death from cerebral infarction in OC users. A recent United States collaborative study of 598 nonpregnant women aged 15 to 44 with stroke demonstrated a 9-fold increase in relative risk of cerebral ischemia or thrombosis for women who use OC compared with those who do not. Users had 2.3 times the risk of hemorrhagic stroke. The fact that only 9 percent of the women with "thrombotic" stroke died may explain earlier failure to demonstrate the risk of OC in mortality trends. Though early reports suggested cerebral venous thrombosis would be the major problem, most autopsy or angiographic studies show that it is arterial occlusion.

Vessey estimates that only 100 of every million users of the pill will be admitted to the hospital, and that about five of these die each year from a

thrombotic stroke attributable to the preparations. Against this small but grim chance must be weighed the unknown but similar risk of pregnancy and the availability of safer, if less certain, modes of contraception.

Smokers may be at increased risk from OC. Very incomplete evidence suggests special caution in OC use in women in older age groups, and in those with hypertension, toxemia in a previous pregnancy, or migraine. New or worsening headache may be an indication to terminate therapy, while focal neurologic symptoms are an absolute indication. Physicians should also be alert to the increasing numbers of women on the pill for reasons other than oral contraception, including regulation of menses and control of menopausal symptoms.

ROBERT I. PFEFFER, MD
STANLEY VAN DEN NOORT, MD

REFERENCES

Collaborative Group for the Study of Stroke in Young Women: Oral contraception and increased risk of cerebral ischemia or thrombosis. N Engl J Med 288:871-878, Apr 1973

Vessey MP: Oral contraceptives and stroke. N Engl J Med 288:906-907, Apr 1973

Kjaer M, de Fine Olivarius B, Waarst A: Cerebral ischemic lesions and oral contraception. Dan Med Bull 18:129-137, 1971

Acute Hemiplegia of Childhood

SUDDENLY AND WITHOUT WARNING a previously well child may develop an acute hemiplegia. Other children will occasionally become hemiplegic in the aftermath of fever and prolonged convulsions. Until recently, in both these groups, the mechanism of acute hemiplegia has been obscure. This contrasts with acute childhood hemiplegias in which the cause can frequently be readily established. Hemiplegia in these children is usually due to trauma, either to the brain or the major cerebral vessels; infection; congenital heart disease; coagulation defects or hemoglobinopathies, especially sickle cell anemia.

Advanced neuroradiological techniques have clarified the mechanism of hemiplegia in most patients formerly assigned to an idiopathic category. Cerebral angiography in the well child, who suddenly develops hemiplegia without warning, will nearly always show vascular abnormalities (stenosis, occlusion, thrombosis, abnormal collaterals, arteriovenous malformation, or arteritis). The children with fever, convulsions and residual hemiplegia will rarely have arterial disease and are presumed to have focal encephalitis.

An acute hemiplegia in childhood should be evaluated rapidly. After neurological examination, a blood cell count, a sedimentation rate test, an x-ray study of the skull, an echoencephalogram, an electroencephalogram and a brain scan should be done without delay. If physical findings suggest increased intracranial pressure, spinal puncture is deferred until cerebral angiography would indicate that it would not be hazardous to the patient. In selected patients coagulation studies, hemoglobin electrophoresis and cardiac assessment may be useful. Many patients, particularly those showing continual deterioration, may benefit from early cerebral angiography to define the cause of the hemoplegia more precisely. The procedure should not be done if the patient is so critically ill that it might be dangerous. Studies should utilize the newer techniques of image magnification and subtraction to show whether defects are present.

Following this or a similar protocol will result in a definite diagnosis in most patients. This enables the physician to give parents a realistic prognosis. Generally, the patient with abrupt hemiplegia tends to make full or partial recovery, while the younger child whose hemiplegia follows fever and seizures frequently retains significant neurological sequelae.

SANFORD SCHNEIDER, MD

REFERENCES

Harwood-Nash D, McDonal P, Argent W: Cerebral arterial disease in children—An angiographic study of 40 cases. Am J Roentgenol Radium Ther Nucl Med 111:672-686, Apr 1971

Solomon G, Hilal S, Gold A, et al: Natural history of acute hemiplegia of childhood. Brain 93:107-120, 1970

Levy A: Acute hemiplegia in childhood—A review of the literature. Clin Proc Child Hosp DC 28:87-99, Mar 1971

Slow Virus Infections of the Central Nervous System

IN THE 1950's, Dr. Bjorn Sigurdsson, an Icelandic veterinarian and virologist, described several "slow" viral infections in Icelandic sheep, some involving only the central nervous system (CNS). He defined a slow infection as one in which the agent multiplies slowly over a course of months or years, producing progressive clinical symptoms usually with a very long incubation period and often localized to a single organ. Fever and blood and tissue changes classically associated with infections were usually absent in these disorders.

In 1957 Dr. D. Carleton Gadjusek began studying kuru, a progressive "degenerative" CNS

disease found only in the Fore people, a Stone Age group living in a small area of New Guinea. The disease ran its afebrile six to twelve month fatal course without laboratory or pathologic evidence of infection. Suspecting kuru might be a slow virus infection, Dr. Gadjusek and colleagues succeeded in transmitting the disease to chimpanzees by intracerebral inoculation with brain suspensions from kuru patients. The incubation period was 18 to 30 months. Subsequently the same investigators transmitted Cruetzfeldt-Jakob disease to chimpanzees by the same method. Cruetzfeldt-Jakob disease is a rare, progressive and fatal human central nervous system disorder of worldwide distribution. In some respects it is neuropathologically similar to kuru. Although no virus particles have been identified in these two diseases using an electron microscope, there seems little doubt that kuru and Cruetzfeldt-Jakob disease are slow virus infections.

Two other slow virus diseases of the human central nervous system have been identified to date. Subacute sclerosing panencephalitis is a progressive neurologic disorder of childhood and adolescence with variable inflammatory changes and neuronal intranuclear inclusions pathologically. This disease is accompanied by high levels of measles antibody in serum and recently measles-like viruses have been isolated from brains of patients with the disease. Progressive multifocal leukoencephalopathy is a rare neurologic disorder, occasionally seen alone but usually occurring when there is impaired immunologic competence as in patients with lymphoma, leukemia, sarcoid or tuberculosis. Demyelination is the prominent pathologic finding. Virus particles suggestive of a papovavirus have been demonstrated by electron microscopy and there have been recent reports of isolation of papovaviruses from diseased brains.

Other chronic neurologic diseases currently under investigation as possibly slow virus infections include amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's and Pick's diseases, and multiple sclerosis.

J. Carroll Ramseyer, MD

REFERENCES

Sigurdsson B: Observations on three slow infections of sheep—I. Maedi, slow progressive pneumonia of sheep: Epizoological and pathological study; II. Paratuberculosis (Johne's disease) of sheep in Iceland: Immunological studies and observations on its mode of spread; III. Rida, chronic encephalitis of sheep with special remarks on infections which develop slowly and some of their special characteristics. Br Vet J 110:255-270, 307-322, and 341-354, 1954

Gadjusek DC: Slow virus diseases of the central nervous system. Am J Clin Pathol 56:320-332, 1971

Weiner LP, Johnson RT, Herndon RM: Viral infections and demyelinating diseases. N Engl J Med 288:1103-1110, 1973

Aspirin and Transient Cerebral Ischemic Attack

It is possible that aspirin may be an effective new weapon in the treatment of some patients with transient cerebral ischemic attack (TIA).

A TIA is an episode of focal neurologic dysfunction due to compromised cerebral blood flow. It clears within an interval arbitrarily considered to be less than 24 hours. Since many patients whose neurologic dysfunction lasts more than an hour have persistent subtle deficit, many so-called TIAs may represent small strokes.

Rational therapy depends upon knowing the cause of the TIA. Treatable causes of transient neurologic deficit include: (1) systemic circulatory failure due to orthostatic hypotension (drugs, cerebral disease, carotid sinus hypersensitivity) or to cardiac pump failure (arrhythmia, Stokes-Adams attacks, myocardial infarction); (2) narrowing of extracranial cerebral arterial supply (by atherosclerotic plaque, or perhaps by neck vessel compression by osteophytes); (3) secondarily altered hemodynamics (anemia, polycythemia, thrombocythemia, paraproteinemia) and (4) embolism from cardiac and extra-cardiac sources. Severe sustained or paroxysmal hypertension may have focal manifestations. Hypoglycemia, migraine and epilepsy may stimulate TIA. The patient with no obvious or treatable cause for TIA may be the one in whom anticoagulants are considered.

To be recommended, any therapy must improve upon the natural history of the disease, which is quite good. In one series, half of 82 patients who were seen for TIA and who received no treatment had subsequent strokes; however, after an average of 40 months, only 20 percent had significant disability. In Marshall's series of 61 patients who were presented with TIA, only one had a stroke during more than four years' average follow-up without therapy. If these patients are to be treated, what is the goal—prevention of recurrent TIAs, of stroke, of death or of all three? TIAs may not be disabling, and myocardial infarction, rather than stroke, is the major cause of death in many series.

Recent enthusiasm for the use of aspirin depends upon its ability to inhibit platelet adhesion and the postulated importance of platelets in arteria, thromboembolism, and some cases of stroke or TIA. The use of aspirin alone did not decrease the frequency of stroke or myocardial

infarction in an elderly population, but TIA was not considered. Dipyridamole, an inhibitor of platelet aggregation, decreased the frequency of TIA or amaurosis fugax in one small series of cases.

Until the outcome of a large collaborative trial of aspirin (W. Fields, unpublished study) now in progress is known, the use of aspirin in TIA is experimental. Benefits to be expected may be fewer attacks with or without significantly altered rates of subsequent stroke or death. Prolonged bleeding time may last for from 1 to 5 days. Patients should be observed for gastrointestinal, spinal epidural or intracranial hemorrhage. In completed stroke or stroke-in-evolution, anticoagulants are contraindicated. Most consultants defer their use for embolic stroke until the fourth or fifth day to avoid hemorrhage. Contraindications to aspirin in these circumstances have not been determined.

ROBERT I. PFEFFER, MD
STANLEY VAN DEN NOORT, MD

REFERENCES

Weiss JH: Thromboembolism—A continuing challenge. N Engl J Med 283:1341-1342, 1970

McDowell FH, Brennan RW (Eds): 8th Conference on Cerebral Vascular Disease. New York, Grune and Stratton, 1973, pp 281-311

Harrison MJG, Marshall J, Meadows JC, et al: Effect of aspirin in amaurosis fugax. Lancet 2:743-744, 1971

Heikinheimo R, Jarvinen K: Acetylsalicylic acid and arteriosclerotic-thromboembolic diseases. J Am Geriatr Soc 19:403-405, 1971

Dilantin® and Laboratory Results

DIPHENYLHYDANTOIN (DILANTIN®) has enjoyed such widespread use and has produced so few significant side effects in most patients that one is prone to forget its role in the unexpected abnormal laboratory result. At times it may interfere directly in methods of measurement. Its inhibitory effect on the growth of Lactobacillus casei in the bioassay of folate causes a reported result lower than the true concentration. Its effects in altering binding affinity increases the uncertainty of protein competitive binding methods as is used in measuring thyroxine. Or it may interefere with the chromagen in a colorimetric method such as the one used in screening for barbiturates.

But most of the effects seen on laboratory data are real changes in the concentration of the constituents measured. They are related to drug-induced alterations in the physiology of the patient. A decrease in glucose tolerance is produced by diphenylhydantoin-inhibition of insulin release. Hepatotoxity causes a variety of changes in liver function tests. *In vivo* alteration of protein-binding affinity distorts most of the thyroid function tests. Hematologic effects are at least in part due to folate deficiency related to the decrease in availability of dietary folate produced by the drug. Many of the measurements of adrenocortical steroids are affected because of the shift in steroid metabolic pathways diphenylhydantoin causes.

There is no need for further examples. The warning is clear. Every clinician must be aware of such possibilities whenever he encounters unexpected abnormal test results. For his assistance, several recent compendia of drug-induced alterations of laboratory data are available. In using them one must recognize that even the most exhaustive listing is still incomplete and that many of the effects noted are dose related. The actual alterations in an individual case may be so slight that they are insignificant clinically, or they may be great enough to cause a mistake in diagnosis if the true cause remains undetected.

RODNEY E. WILLARD, MD

REFERENCES

Constantino NV, Kabat HF, Hugh F: Drug-induced modification of laboratory test values—Revised 1973. Am J Hosp Pharm 30:24-71, Jan 1973

Hansten PD: Drug Interactions. 2nd Edition, Philadelphia, Lea & Febiger, 1973

Martin EW: Hazards of Medication. Philadelphia, J. B. Lippincott Co, 1972

Young DS, Thomas DW, Friedman RB, et al: Bibliography: Drug interferences with clinical laboratory tests. Clin Chem 18: 1041-1303, Oct 1972

Tardive Dyskinesia

TARDIVE DYSKINESIA is one of the adverse effects that may result from the use of phenothiazines and some other antipsychotic medications. It usually consists of persistent, slow, purposeless movements of the tongue, lips and jaw, but bizarre movements of other portions of the body may occur. Although the abnormal movements are relatively mild in many persons, they may be severe enough to resemble Huntington's chorea or dystonia, and may be disabling.

Tardive dyskinesia usually occurs during therapy with phenothiazines but may occur after the medication has been discontinued. Rarely, the symptoms persist for months or even years. Although the frequency of this syndrome is not very great, it does appear to be greater in elderly patients and when high dosages of phenothiazines

are used. However, it occasionally occurs with low dosage or short-term therapy. A recent Food and Drug Administration bulletin suggests that fine vermicular movements of the tongue may be any early sign of tardive dyskinesia and that the complete syndrome may not develop if medication is stopped immediately. Drug "holidays" are advised for patients receiving long-term therapy and if abnormal movements are observed the drug should not be started again.

Phenothiazines are among the most widely used and most effective drugs available for treatment of some psychoses and are effective in treatment of certain other conditions as well. The development of tardive dyskinesia is distressing to both the patient and the physician but the possibility that it may occur should not prevent the use of phenothiazines and other antipsychotic drugs when they are indicated. Early recognition of this complication and prompt discontinuance of the offending drug may prevent the more serious manifestations.

GUY M. HUNT, MD
DONALD I. PETERSON, MD

REFERENCES

Crane GE: Clinical psychopharmacology in its 20th year. Science 181:124-128, Jul 1973

FDA Drug Bulletin. Bureau of Drugs, FDA, DHEW, Rockville, May 1973

Opsoclonus, Myoclonus, Ataxia and Occult Neuroblastoma (Neuroblastoma—Encephalopathy)

REPORTS OF YOUNG CHILDREN with acute cerebellar ataxia have appeared in the literature for decades. These case reports have included patients who, in addition to ataxia, had "tremors" of the limb and trunk and "violent tremors" of the extraocular muscles. Kinsbourne called attention to six children, all with similar findings of irregular jerking of limb and trunk and a chaotic, irregular eye movement. The cause was unknown and he called this condition myoclonic encephalopathy of infants. Solomon and Chutorian reported two small children with opsoclonus and occult neuroblastoma and, citing a reference to an adult patient with opsoclonus, myoclonus, ataxia and occult bronchogenic carcinoma, questioned whether there was an association between opsoclonus and occult neuroblastoma. The association of these neurological signs and occult neuroblastoma in small children was soon recognized by others and additional reports appeared in the literature.

The patients were young children who had sudden onset of limb and truncal ataxia without papilledema or other signs of increased intracranial pressure. At the same time, or shortly thereafter, myoclonus of varying severity appeared involving the limbs and, on occasion, the trunk. Eye movements typical of opsoclonus are characterized by gross irregular chaotic multidirectional conjugate jerks. This ocular agitation is intermittently present throughout the day and is occasionally seen during sleep, but of diminished amplitude.

The striking combination of clinical findings—opsoclonus, myoclonus and ataxia should alert the physician to the possible presence of an occult neuroblastoma. The diagnosis is commonly made by simple diagnostic tests including plain roentgenograms of the chest and abdomen and occasionally an intravenous pyelogram. Other diagnostic tests include urinary assay for vanillyl mandelic acid and cystathionine.

Treatment includes surgical removal of the neuroblastoma, radiation therapy to the tumor site and tumor chemotherapy. Symptomatic relief from opsoclonus and myoclonus has been achieved in some patients by administration of adrenocorticotropic hormone or prednisone.

The relationship of neuroblastoma and the abnormal neurological findings is not yet explained. Possible pathogenic mechanisms considered have included (1) some unknown oncogenic agent, (2) an immunological mechanism wherein the neuroblastoma acts as an antigen, and (3) the possibility that the neuroblastoma produces excessive catecholamines which in turn are toxic in some way to the cerebellar or central nervous system structures.

The clinical course of this neuroblastoma-encephalopathy is varied, ranging from complete disappearance of all signs and symptoms of disease to death. A significant number of children who survive, however, have some neurological sequelae or psychomotor retardation.

BRUCE O. BERG, MD

REFERENCES

Kinsbourne M: Myoclonic encephalopathy of infants. J Neurol Neurosurg Psychiatry 25:271-276, 1962

Solomon G, Chutorian A: Opsoclonus and occult neuroblastoma. N Engl J Med 279:475-477, 1968

Ross AT, Zeman W: Opsoclonus, occult carcinoma and chemical pathology in dentate nuclei. Arch Neurol 17:546-551, 1967

Bray P, Ziter F, Lahey E, et al: The coincidence of neuroblastoma and acute cerebellar encephalopathy. J Pediatr 75:983-990, Dec 1969

The Lymphocyte and Multiple Sclerosis

MANY INVESTIGATORS consider an exogenous agent as the primary etiologic factor in the development of multiple sclerosis (MS). However, delayed hypersensitivity involving antigens of the central nervous system is the hypothesized pathogenetic mechanism responsible for the clinical expression of the disorder.

Two aspects related to delayed hypersensitivity have been demonstrated in multiple sclerosis which support this model of pathogenesis, namely (1) evidence of host sensitization to encephalitogenic protein which may result in lymphocytes capable of damaging myelin and (2) a lymphotoxic factor which may represent a bodily defense from self-destruction.

In vitro techniques for the detection of delayed hypersensitivity are well established. Upon exposure to specific antigens, a sensitized population of lymphocytes will undergo morphological transformation into lymphoblast-like cells with associated increases in deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and protein synthesis. The release of several functionally distinct lymphocyte products, such as macrophage migration inhibition factor (MIF), appears to be the culmination of this complex biochemical process.

In the presence of encephalitogenic protein, the putative antigen of multiple sclerosis, peripheral blood lymphocytes of MS patients experience these same morphological and biochemical alterations. It has also been demonstrated that such lymphocyte stimulation results in the elaboration of MIF. These experiments do help substantiate the theory of autoimmunity in MS, as did the earlier study by Berg and Källen. Their work established that lymphocytes from ME patients during exacerbation could exert a toxic effect on neurologia in tissue culture. However, it must be noted that disparate results have been reported concerning the morphological and metabolic changes of MS lymphocytes stimulated by encephalitogenic protein.

The complex association of the lymphocyte and MS is further obscured by the recent description of a transiently appearing serum protein which is specifically toxic to lymphocytes. The toxic effect of this heat-stable, small molecular weight protein is exerted through inhibition of DNA-directed RNA synthesis within the lymphocyte. The presence of this lymphotoxic factor is most commonly detected during exacerbation of multiple sclerosis. Therefore, it has been suggested that this factor may be the result of a host-defense relation against self-destruction.

GREGORY WHITE, MSR II
STANLEY VAN DEN NOORT, MD

REFERENCES

Stjernholm RL, Wheelock EF, van den Noort S: A lymphotoxic factor in multiple sclerosis serum. J Reticuloendothel Soc 8:334-341, Oct 1970

Bartfeld H, Atoynatan T: Lymphocyte transformation in multiple sclerosis. Brit Med J 2:91-92, Apr 11, 1970

Berg O, Källen B: Effect of mononuclear blood cells from multiple sclerosis patients on neuroglia in tissue culture. J Neuropath Exp Neurol 23:550-559, Jul 1964

Cerebral Death Criteria

CONCEPTS AND DEFINITIONS of death have come under increasing discussion in recent years. This has largely resulted from improved resuscitation techniques and the development of life support systems which may at times leave patients with devastating brain damage, some in irreversible coma. Although in a state of "cerebral death," they may not meet the traditional criteria of "systemic death," such as irrevocable absence of heartbeat. The ability to preserve the patient in this mechanically maintained state poses frequent problems in the widespread use of organ transplants. It also presents the physician and family with a dilemma having ethical, moral, legal and financial repercussions. These matters are as yet unresolved.

The most widely held definition of irreversible coma appeared in 1968 and has become known as the "Harvard Criteria." There have been some subsequent refinements to the original definition which still basically is as follows: (1) Unreceptivity and unresponsivity to external (verbal and painful) stimuli; (2) No spontaneous movement or spontaneous respirations; (3) Absence of reflexes (deep tendon, plantar, corneal, pharyngeal reflexes), fixed dilated pupils, absence of eye movements even with ice water irrigation of the ear canals; and (4) A flat electroencephalograph (a linear or isoelectric electroencephalogram tracing) which is of great confirmatory value. Technical standards were described in order that the test be properly performed.

These features were to be rechecked 24 hours later and were not to have changed in that period. The validity of the diagnosis of irreversible cerebral dysfunction was dependent on the exclusion

of two conditions: The absence of hypothermia (temperatures below 90°F or 32°C) and the absence of central nervous system depressant drugs.

Evaluation of these clinical and laboratory signs may be difficult or confusing. Spinal cord activity may result in increased tone or the appearance of some deep tendon reflexes mistakenly interpreted as being of cerebral origin. At times the electroencephalograph may be obscured, especially in intensive care units where artifacts are produced by electrical and mechanical equipment.

Additional techniques are under investigation in order to improve the diagnosis of irreversible cerebral dysfunction. These include the monitoring of cerebral blood flow. The absence of a detectable radioisotope bolus is said to correlate well with the clinical and isoelectric evidence of cerebral death and may further reduce the possibility of a diagnostic error.

Regardless of technical diagnostic advances, the profession and society at large will have to resolve the next question of applying these neurologic standards to the broader legal and humane definition of death.

EDWARD H. DAVIS, MD

REFERENCES

A definition of irreversible coma—Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. JAMA 205:337-340, 1968

Refinements in criteria for the determination of death: An appraisal—A report by the Task Force on Death and Dying of the Institute of Society Ethics and the Life Sciences. JAMA 221: 48-53, 1972

Korein J: On cerebral, brain and systemic death. Current Concepts of Cerebrovascular Disease—Stroke (Bull Am Heart Assn) 8:9-14, May-Jun 1973

Fletcher J: New definitions of death. Prism 2:13-14, 1974

ADVISORY PANEL TO THE SECTION ON NEUROLOGY

EDWARD H. DAVIS, MD, *Chairman, Beverly Hills*

EDWARD SHEV, MD
CMA Section on Neurology, Chairman
San Francisco

JAMES R. NELSON, MD
CMA Section on Neurology, Secretary
La Jolla

PIERRE DREYFUS, MD
CMA Section on Neurology,
Assistant Secretary
University of California, Davis

ROBERT I. PODOSIN, MD
CMA Scientific Board
Los Angeles

J. CARROLL RAMSEYER, MD
Los Angeles

GUY M. HUNT, MD
Loma Linda University

DAVID PRINCE, MD
Stanford University

AUGUSTUS S. ROSE, MD
University of California, Los Angeles

BRUCE O. BERG, MD
University of California, San Francisco

J. P. VAN DER MUELEN, MD
University of Southern California
Los Angeles

JACK M. MOSIER, MD
Long Beach

BYRON C. PEVEHOUSE, MD
San Francisco

J. DONALD EASTON, MD
University of California, San Diego

ARNOLD STARR, MD
University of California, Irvine
California College of Medicine

EDITORIAL

The Rule of Wal

ONCE UPON A TIME there was a country which overthrew its king and decided to live under The Rule of Wal. The people themselves would make the rules which would govern them and the rules were called Wals. Because the people made the wals there was great attention paid to the rights and freedom of individual citizens and to the common good, and it was considered very important that everyone obey the wals. In this way a great nation was founded.

As time went by the nation prospered and the number of wals increased greatly, and so did the number of reasons for which wals were enacted. A large number of professionals called walyers came into being and it came to pass that they virtually took over The Rule of Wal, although they continued to act in the name of the people. As the walyers increased the numbers of wals and extended their scope, two very important things began to happen.

The first thing that happened was that there came to be so many wals that they could not all be enforced or obeyed at the same time, and everyone from the leader of the country to the plain citizens and even the students in the schools began to choose which wals they would obey and which they would not, and The Rule of Wal itself began to choose which wals it would try to enforce and which it would not. This led to many problems and considerable disorder within The Rule of Wal and the walyers were kept very busy since they had long since brought it about that only they, the walyers, could represent the citizens or The Rule of Wal itself in disputes in the courts of the country.

The second thing that happened was that The Rule of Wal and the walyers began to try to regulate human society and even human nature by enacting wals, and this they could not make work. However, the walyers never quite believed that it would not work, and they kept on enacting more wals which kept on not working. This is what happened when they tried to regulate the nation's economy by enacting wals, and it happened again when they tried to regulate the people's health, also by enacting wals.

Nobody seemed to give much thought to the reasons why the wals did not work, and nobody stopped to think that the wals and even the way The Rule of Wal was administered might not be appropriate for the very complex and interdependent technologic, social, economic and political system which had developed in the great nation. The fact which many had forgotten was that The Rule of Wal had been rooted in a primitive and quite historic adversary approach to solving problems and disputes which was a method known to have worked well in ancient times in simpler societies with simpler problems which were amenable to quite simplistic solutions. And the truth which nobody seemed to recognize was that the ancient adversary approach was simply too naive and simplistic to meet the needs of a modern human society living in a biologically, socially, economically and politically interdependent world. Actually the very opposite of an adversary approach was what was needed but nobody seemed to understand this.

Unfortunately the great nation which had overthrown its king and accepted The Rule of Wal went into bad times. It was to be many years before very much thought would be given to why the times were bad, either by the walyers who were trying to administer The Rule of Wal or by the people who really wanted to live by it. It was only when they did give thought to it, and after they had rejected the ancient adversary approach and replaced it with another more appropriate to the needs of their very complex and interdependent society, that the friction within their technologic, social, economic and political system began to lessen and another era of great progress came to pass for the great nation which had chosen to live under The Rule of Wal.

And curiously enough it turned out that the physicians of the country were among the very first to see the need for change because the adversary approach of The Rule of Wal had proved unhealthy for the care of the sick and for the health care of the nation as a whole.

—MSMW

Immunity to Reinfection in Patients with Gonorrhea

Of all the factors implicit in the control of gonococcal infection, none is quite so puzzling as the apparent failure of an attack of gonorrhea to confer protective immunity. The problem is more obvious in men, who are likely to seek medical attention for local genitourinary symptoms. Women are usually asymptomatic. Even in men, absence of immunity is not absolute. Mahoney and his co-workers showed many years ago that volunteers with a history of gonorrhea were more difficult to infect experimentally than those who had never had the infection.[1] Still, lack of protection appears to be the rule, although the possibility cannot be eliminated that patients with repeated infections represent a unique immunologic subpopulation of all those who acquire gonorrhea.

It is not as if the immune system ignores the gonococcus. Infection with Neisseria gonorrhoeae is associated with an immune response that is both local and systemic, and cellular and humoral. The paradox lies in the apparent failure of protection despite every evidence of appropriate immune recognition.[2]

The first step in the establishment of gonococcal infection is attachment of the microorganism to a susceptible mucosal surface. Adherence appears to be mediated by pili (fimbria) which are hairlike proteinaceous appendages found on virulent T-1 and T-2 (small colony type) gonococci, but not on T-3 and T-4 avirulent (large colony type) gonococci. However, pili cannot be the only determinant of local invasiveness because many nonpathogenic Neisseria species (N. catarrhalis, N. flavescens) are also pilated.[3] Local immune response to the gonococcus is manifested by the prompt appearance of gonococcus-specific gamma A immunoglobulin (IgA) and secretory IgA antibody in the urethral exudate.[4] Although IgA is not known to have a direct effect on the gonococcus, there is evidence from other experimental systems that IgA serves to prevent the adherence of microorganisms to mucosal surfaces.[5] There are unfortunately no direct *in vitro* studies to indicate whether gonococcal IgA antibody can prevent adhesion of N. gonorrhoeae to mucosal cells. However, clinical observations suggest that local IgA antibody is not protective against reinfection.

In addition to their ability to tether gonococci to mucosal cells, pili also subserve an important antiphagocytic function.[6,7] This is paradoxical, because pili also bind gonococci to the surface of phagocytic leukocytes. Thus the very structures which bring gonococci and leukocytes into contact serve to prevent phagocytosis. The situation is not unique, however; the M protein of streptococci behaves in a nearly identical fashion.[7] If pili are antiphagocytic, how then can one explain the presence of myriads of intracellular gonococci in urethral exudate? One possible explanation is "surface phagocytosis," the phenomenon wherein phagocytosis is enhanced by the crowding of microorganisms and leukocytes in a setting such that bacterial trapping against a surface (for example, another leukocyte) supplements or supplants the need for opsonic antibody.[8] Although there are no direct data concerning the viability of gonococci within polymorphonuclear leukocytes (PMN) of the urethral exudate, it is generally assumed that such bacteria are dead.

At the systemic level, there is an impressive humoral immune response to local and disseminated gonococcal infection. Gamma G immunoglobulin (IgG), gamma M immunoglobulin (IgM), and IgA antibodies with antigonococcal specificity appear in the blood following infection, but seldom persist in high titer more than a few weeks or months.[9,10] Antibody activity has been shown using a variety of antigens (sonicates of whole gonococci, alkaline extracts, protoplast antigens and so forth) and a variety of techniques (complement fixation, microprecipitation, opsonization, hemagglutination, hemagglutination inhibition, immunofluorescence and so forth). Particular excitement has arisen with the demonstration by Buchanan and his co-workers, using a quantitative radioactive antigen-binding assay technique, of antipilar antibody in the sera of asymptomatic female gonococcal carriers and patients of both sexes with a history of recurrent gonococcal infection.[11]

Except for its opsonic activity, serum antibody

to N. gonorrhoeae is probably not protective against infection. This was not always considered to be the case, for the work of Spink and Keefer in 1937 suggested that gonococci were susceptible to the lytic activity of human immune serum and complement.[12] Recently, Ward, Watt and Glynn have shown that antibody-complement susceptibility is an attribute of passaged gonococci, while freshly isolated gonococci possess a surface component that renders them resistant to lysis.[13] Resistance can be reconferred on passaged strains by culturing them on agar containing an extract of human prostate.[14] Whether prostatic extract provides an additional virulence factor that is lost on subculture or merely allows synthesis of a hardier cell wall remains to be determined. Provided gonococci are appropriately opsonized, they appear to be readily ingested and killed by PMN's.[8] There is virtually no evidence to support a failure of the PMN in the lack of immunity conferred by gonococcal infection.

Evaluation of the role of cell-mediated immunity in gonorrhea has begun, and several investigators have shown that lymphocytes from infected patients undergo blastogenesis when exposed to sonicates of T-1 gonococci or their alkaline extracts.[2,15,16] However, lymphocytes are not phagocytic cells; there is compelling evidence that macrophages show enhanced bactericidal activity under the direction of lymphocytes or their soluble lymphokines. The role of human monocytes and their derivative macrophages in defense against gonorrhea has been largely unexplored although our own unpublished data indicate that isolated human monocytes and macrophages kill T-1 and T-4 gonococci as well as PMN's. Further, since lymphocyte recognition of gonococci is intact in most patients with gonorrhea, it is unlikely that important defects exist at the macrophage antigenic "processing" step of cell-mediated immunity.

The foregoing data suggest that gonococcal immunity in patients with repeated infection is intact and appropriate. Why, then, are patients susceptible to reinfection? There are at least two principal possibilities:

- Immunity to N. gonorrhoeae may be type specific. There is great interest at present in serotyping gonococci. In one approach, Glynn and Ward have shown that passaged gonococci can be divided into at least four groups on the basis of the complement-dependent bactericidal reaction. The bactericidal antibodies could be absorbed with red blood cells coated with gonococcal lipopolysaccharide.[17] In a totally different approach to typing, Carifo and Catlin have divided clinical isolates of gonococci into at least 22 auxotypes, an auxotype being defined as a microorganism with a distinctive nutritional profile on defined medium.[18] There are currently no promising methods for differentiating gonococci on the basis of susceptibility to bacteriophages or bacteriocins. With regard to antipilar antibody, it is interesting that the studies of Buchanan and his co-workers show no apparent major antigenic differences among gonococcal pili from different strains.[11] A putative opsonic antipilar antibody, then, should protect regardless of the serotype of the infecting strain, if indeed antipilar antibody plays a direct role in protection.

- Venereally transmitted microorganisms are unique in that transmission is usually accomplished in the presence of seminal secretions. The effect of semen upon the infecting microorganism and upon the interaction between microorganism and epithelial surface, and microorganism and leukocyte has not been explored. All factors in gonococcal-cell interaction *in vitro* have been defined under conditions which ignore the effects of seminal fluid and vaginal secretions. It has been reported recently that gonococci may attach to spermatozoa.[19] The significance of such attachment is not clear since pilated gonococci also attach to red blood cells, buccal mucosal cells, amnion cells and phagocytes *in vitro*. Nevertheless, the approach is an important one. Is it possible that components of semen might coat gonococci and interfere locally with opsonic or phagocytic function? What is the effect of seminal secretions on the putative ability of secretory IgA antibody to block bacterial adhesion to cells? These questions are central to any investigation of host response to venereally transmitted microorganisms, and appropriate data are badly needed.

DAVID J. DRUTZ, MD
Associate Professor of Medicine
Chief, Division of Infectious Diseases
University of Texas Health Science Center
San Antonio

REFERENCES

1. Mahoney JF, Van Slyke CJ, Cutler JC, et al: Experimental gonococcic urethritis in human volunteers. Am J Syph Gonor & Ven Dis 30:1-39, 1946

2. Kearns DH, Seibert GB, O'Reilly RJ, et al: Paradox of the immune response to uncomplicated gonococcal urethritis. N Engl J Med 289:1170-1174, 1973

3. Wistreich GA, Baker RF: The presence of fimbriae (pili) in three species of Neisseria. J Gen Microbiol 65:167-173, 1971

4. Kearns DH, O'Reilly RJ, Lee L, et al: Secretory IgA antibodies in the urethral exudate of men with uncomplicated urethritis due to Neisseria gonorrhoeae. J Infec Dis 127:99-101, 1973

5. Williams RC, Gibbons RJ: Inhibition of bacterial adherence by secretory immunoglobulin A: A mechanism of antigen disposal. Science 177:697-699, 1972

6. Punsalang AP Jr, Sawyer WD: Role of pili in the virulence of Neisseria gonorrhoeae. Infec Immun 8:255-263, 1973

7. Ofek I, Beachey EH, Bisno AL: Resistance of Neisseria gonorrhoeae to phagocytosis: Relationship to colonial morphology and surface pili. J Infec Dis 129:310-316, 1974

8. Thongthai C, Sawyer WD: Studies on the virulence of Neisseria gonorrhoeae—I. Relation of colonial morphology and resistance to phagocytosis by polymorphonuclear leukocytes. Infec Immun 7:373-379, 1973

9. Cohen IR, Kellogg DS Jr, Norins LC: Serum antibody response in experimental human gonorrhoeae immunoglobulins G, A, and M. Br J Vener Dis 45:325-327, 1969

10. Welch BG, O'Reilly RJ: An indirect fluorescent-antibody technique for study of uncomplicated gonorrhea—I. Methodology. J Infec Dis 127:69-76, 1973

11. Buchanan TM, Swanson J, Holmes KK, et al: Quantitative determination of antibody to gonococcal pili—Changes in antibody levels with gonococcal infection. J Clin Inves 52:2896-2909, 1973

12. Spink WW, Keefer CS: Studies of gonococcal infection—11. The bacteriolytic power of the whole defibrinated blood of patients with gonococcal arthritis. J Clin Inves 16:177-183, 1937

13. Ward ME, Watt PJ, Glynn AA: Gonococci in urethral exudates possess a virulence factor lost on subculture. Nature 227: 382-384, 1970

14. Watt PJ, Glynn AA, Ward ME: Maintenance of virulent gonococci in laboratory culture. Nature New Biol 236:186-187, 1972

15. Esquenazi V, Streitfeld MM: Transformation of lymphocytes in gonorrhea before and after therapy. Infec Immun 8:503-509, 1973

16. Kraus SJ, Perkins GH, Geller RC: Lymphocyte transformation in repeated gonococcal urethritis. Infec Immun 2:655-658, 1970

17. Glynn AA, Ward ME: Nature and heterogeneity of the antigens of Neisseria gonorrhoeae involved in the serum bactericidal reaction. Infec Immun 2:162-168, 1970

18. Carifo K, Catlin BW: Neisseria gonorrhoeae auxotyping: Differentiation of clinical isolates based on growth responses on chemically defined media. App Microbiol 26:223-230, 1973

19. James-Holmquest AN, Wende RD, Williams RP: Attachment to human sperm by piliated and non-piliated Neisseria gonorrhoeae. Paper presented at the Diamond Jubilee Mtg. of the American Society for Microbiologists, Chicago, May 12-17, 1974

Instant Acupuncture for Nevada

Dr. William Edwards has presented in this issue an excellent chronological account of the development of legislation on acupuncture and Chinese medicine in the state of Nevada and the manner in which it is going forward at present. However, he has not sufficiently emphasized the type of tactics used to get this legislation passed by practically a stampede vote and also has made little mention of the rejection by the legislators of offers of advice or consultation from the regular medical profession.

On March 12, 1973, SB 420, allowing demonstration of acupuncture, was introduced in the Nevada state Senate as an emergency bill by the Committee on Health, Welfare, and State Institutions in mimeograph form and without printing, reading or discussion. It was passed unanimously and was sent to the Assembly, which passed it on March 13, 1973. As noted in the article, a previous request to the Nevada State Board of Medical Examiners to license an acupuncturist for demonstrations had been rejected by the Board. The Board considered diagnosis and acupuncture to be the practice of medicine and the demonstration was to be performed by a person not a registered physician, not a United States citizen and not presenting adequately documented proof of any kind of training. Both this and the final bill that followed were passed in an atmosphere of great haste. The fact that it was not even publicly read before passage indicates the amount of legislative thought put into it.

True, there were messages and telephone calls to the Governor, legislators and doctors from people in Nevada and other states wishing to be treated by acupuncture. Whether many of these letters were stimulated by a public relations firm or other interested parties is not known. What is known, however, is that Mr. Arthur Steinberg, an attorney from New York and Las Vegas spent sums of money and much time to push this legislation. A strong public relations firm from Las Vegas was employed before and during legislative sessions, and the firm's employees spent much time in Carson City exerting almost constant pressure. As might have been expected, their utterances did not carefully set forth the opposite views of the medical profession. Moreover, although there was little public demand for traditional Chinese medicine and herbalism in addition to acupuncture, Mr. Steinberg and his associates, the lobbyists and the legislative proponents appeared to want the three as one package. This approach was propelled to a conclusion with little time for careful consideration.

Representatives of the Nevada State Medical Association appeared before the Senate Health, Welfare, and State Institutions Committee in regard to the final bill, SB 448, and a summary of their position was expressed by Dr. John Sande, President of the Nevada State Medical Association, as follows:

> "It is the earnest belief of the physicians of the State of Nevada that the practice of acupuncture should be evaluated and carefully studied under a research program to determine its actual benefits and potential hazards. This will ensure the patients' welfare will be the prime consideration. This could be accomplished without denying the patient access to this form of therapy. The medical association feels that in the nearly two years before the next session of the legislature, valuable infor-

mation could be obtained and acupuncture and other forms of Chinese Medicine studied in proper prospective."

The State Medical Association presented essentially the same argument to the Committee on Health and Welfare of the Assembly, but the bill was quickly passed by both houses of the state legislature with only two dissenting votes. However, at the request of the State Medical Association, the provision that a physician or two be on the Board of Chinese Medicine, was amended to omit the physicians because the State Medical Association felt that the bills proposed might easily lead to exploitation of the public pocketbook while at the same time not safeguarding the health of the public. The Governor, however, felt this omission questionable on the grounds that any serious health problems that might occur could reflect badly if there were not some doctors of medicine on the board. Therefore, two physicians were appointed to the Board of Chinese Medicine although this was not required by law. As the bill passed both houses of the legislature almost unanimously, the Governor (whatever his own personal reservations about the quality of the bill) had little choice other than to sign it.

Following enactment, the Governor has made a very praiseworthy attempt to have the provisions of the act carried out in as responsible a manner as possible.

Dr. Sande states, relative to the bill as passed in Nevada,

> "On November 18, 1973 when State Senator Lee Walker of Nevada, introducer of the Chinese Medicine Bill, appeared before the program of Acupuncture Theories and Practice in Politics, at UCLA, to present the Nevada law on acupuncture, he received considerable criticism from a prominent member of the California State Legislature noting that Nevada and not California had passed this law in such haste. Senator Lee Walker at that time stated that he regretted some of the provisions of the law and hoped they could be changed in the future."

However, it should be noted that he did not seek advice or consultation with representatives of the Nevada State Medical Association or with any other doctor so far as is known to the medical profession before introduction of the bill to the legislature.

It is suggested by Dr. Edwards that there should be representation on the board for different schools of oriental medicine, including Japanese and Korean. However, it seems only prudent that this step should be approached very cautiously and should not be taken unless there can be very definite and reliable methods of evaluating the training given by the individual schools. The training background of some of the people who make claims as knowledgeable acupuncturists (such as receiving training in a monastery in the Peoples Republic of China) is often vague and sometimes almost impossible to verify.

Dr. Edwards also states that by 1975 the state should dispense with the advisory committee. However, there is reason to disagree with such a proposed action. This board was established suddenly while other licensing boards have been developed over a period of many scores of years in this country. Whatever emotional reactions the legislative proceeding may have initiated, measures for protecting the health of patients are still highly desirable.

There has recently been strong pressure by some members of the Board of Chinese Medicine and some outside parties to allow a single acupuncturist to have an unlimited number of acupuncture assistants, either all in one clinic or one each in an unlimited number of clinics. This would make proper supervision of diagnosis and treatment impossible. The majority of the board has wisely avoided such unlimited licensing of assistants and it is hoped they will continue to resist this pressure. In this regard, it is interesting to note an amendment to the Nevada State Medical Practice Act dealing with physicians' assistants, also passed by the 1973 Legislature. This amendment, which was requested by the Nevada State Medical Association, states, "A supervising physician shall not cosign for, employ or supervise more than one physicians' assistant at the same time."

Dr. Edwards' article is timely and although this review does not attempt any judgment on the value of acupuncture, the sequence of events in in Nevada should provide material for serious thought on the part of legislators and others in states contemplating legislation dealing with acupuncture and Chinese medicine.

FRED M. ANDERSON, MD
Member, Board of Regents
University of Nevada System
Reno

Recent Advances in the Pathophysiology of Asthma

BRONCHIAL ASTHMA affects millions of Americans, kills 4,000 to 7,000 annually, is exceeded only by mental illness and arthritis as a cause of limited activity, is the most common chronic illness in children less than 17 years old, and costs millions of dollars annually in medical care and days lost from school and work. Until recently, asthma has been ignored largely in the undergraduate curriculum, in training post-graduate physicians and other health workers and in allocation of funds for research. The timely review in this issue of THE WESTERN JOURNAL OF MEDICINE serves as a reminder that much progress has been made in the understanding of this disease.

The traditional concept of asthma assumes that the reaction is entirely a result of direct, local effects in airway tissues.[1] Initial studies of isolated leukocytes suggested that antigens react with specific IgE antibodies (synthesized by B-cell dependent plasma cells) fixed to sensitized cells. This physiochemical reaction initiates a biochemical sequence dependent on divalent ions, glycolytic energy sources, and diisopropylfluorophosphate (DFP)-sensitive esterases leading to secretion of histamine and other chemical mediators. The secretory process appears to be modulated by intracellular levels of cyclic nucleotides. Three types of endogenous hormones (β-adrenergic catecholamines, prostaglandins, and histamine) activate adenylate cyclase to convert adenosine triphosphate (ATP) to cyclic adenosine monophosphate (CAMP) and also inhibit antigen-induced mediator release. These hormone effects are prevented by their respective antagonists and are potentiated by phosphodiesterase inhibitors (for example, methylxanthines) which prevent degradation of CAMP. Similar correlations between increased cellular levels of CAMP and inhibition of mediator release from sensitized leukocytes are observed after cholera enterotoxin. Mediator release is also inhibited by dibutyryl CAMP.

These observations have been extended to antigen-induced release of histamine, and to other mediators from respiratory tissues including passively-sensitized human and monkey lung and from human nasal polyps. The same naturally-occurring hormones increase respiratory tissue CAMP levels and inhibit secretion of mediators. Indirect evidence now suggests that cyclic guanosine monophosphate (CGMP) also serves a regulatory function in this secretory process. The two cyclic-nucleotides may act in a "push-pull" mechanism to regulate responses of lymphocytes, neutrophils and mast cells: sympathetic agonists inhibit function of these cells via CAMP while parasympathetic agonists enhance function via CGMP. Some investigators have proposed, with little direct confirmation, that airway smooth function is regulated in a similar manner.

The relevance of these results to immune responses in the whole organism remains to be determined. The concepts are based on studies of tissues containing many different cell types. During preparation of the lung tissues, receptors in cell membranes may have been exposed which are not normally accessible to hormones *in vivo*. Most studies of lung tissues have utilized parenchyma, devoid of airways or normal autonomic innervation.

In the whole organism, regulation of airway tone is largely dependent on nervous mechanisms: sympathetic nerve stimulation dilates, parasympathetic nerve stimulation constricts airways and the parasympathetic system clearly predominates. There is little evidence of α sympathetic constrictor activity *in vivo*; even studies of isolated airway smooth muscle show quantitatively insignificant responses to α sympathetic agonists in comparison to responses to parasympathomimetic agonists.

On the other hand, many different physical and bronchoactive agents cause vagally-mediated reflex bronchoconstriction. In comparison with healthy persons, asthmatic patients have hyperirritable airways since they respond to the same stimuli with more severe bronchoconstriction than normal persons. Although histamine does cause direct contraction of airway smooth muscle isolated from most species, it causes mainly reflex bronchoconstriction in the intact organism. Furthermore, Widdicombe and coworkers[2] have shown in experimental anaphylaxis, and Gold and coworkers[3] have demonstrated in experimental asthma, that specific antigen induces acute bron-

choconstriction that depends on a vagally-mediated parasympathetic reflex.

Thus in the whole organism, both nervous reflex and biochemical mechanisms may be triggered by antigen-antibody interaction. Future studies should evaluate the relative importance of the cyclic nucleotides and the autonomic nervous system in regulating immune and inflammatory reactions in the whole organism. Such studies may reveal important relationships concerning regulation of many different host defense mechanisms involving T-cell as well as B-cell functions.

Future studies should also focus on the basic defect in asthma. Clearly, Szentivanyi's assumption that normal airway tone is the result of α and β adrenergic interaction is incorrect, although α adrenergic receptor activity may prove to be altered in different diseases. His original proposal that the asthmatic defect is due to partial β blockade is also largely unsubstantiated, particularly since pharmacologically-induced β blockade in healthy subjects does not cause asthma. Present evidence indicates that the asthmatic defect is controlled by a Mendelian dominant gene closely linked to the histocompatability system, but its expression requires other genetic and environmental factors.[4] For example, genetic defects may exist in the control of basal IgE levels, degree of IgE response, mucosal transport of macromolecules, target organ sensitization, mediator release, and even nervous reflex regulation. In pursuing these questions, researchers should increase our understanding of asthma and improve the prospects for therapy of this important disease.

WARREN M. GOLD, MD
Department of Medicine and Cardiovascular Research Institute University of California, San Francisco

REFERENCES

1. Bourne HR, Lichtenstein LM, Melmon KL, et al: Modulation of inflammation and immunity by cyclic AMP. Science 184:19-28, 1974

2. Karczewski W, Widdicombe JG: The role of the vagus nerves in the respiratory and circulatory reactions to anaphylaxis in rabbits. J Physiol 201:293-304, 1969

3. Gold WM, Kessler G-F, Yu DYC: Role of vagus nerves in experimental asthma in allergic dogs. J Appl Physiol 33:719-725, 1972

4. Levine BB, Stember RH, Fotimo M: Ragweed hay fever—Genetic control and linkage to HL-A haplotypes. Science 178: 1201-1203, 1972

CORRECTION

INADVERTENT DROPPING of a line of type from the editorial "National Health Insurance—Are We Really Ready for It Yet?," which appeared in the May issue, left one sentence senseless. The error was made in the first full paragraph on page 409. The third sentence in the paragraph should have read: Such a program must assure that the services rendered will be what are needed and of high quality, that the costs will be reasonable and the funding adequate, and that the program as a whole will not prove so inflationary to the health care system itself, or perhaps even to the national economy, that it will defeat its own aims.

CASE REPORTS

Refer to: Krishnamurthy GT, Blahd WH: Hyperthyroidism in the presence of panhypopituitarism—Thyroid crisis and hypothyroidism following radioiodine treatment. West J Med 120:491-496, Jun 1974

Hyperthyroidism in the Presence of Panhypopituitarism

Thyroid Crisis and Hypothyroidism Following Radioiodine Treatment

G. T. KRISHNAMURTHY, MB, MS
W. H. BLAHD, MD
Los Angeles

FROM A GROUP of more than 350 women who had hypophysectomy for breast cancer, only ten remained euthyroid, all the rest developing hypothyroidism.[1] Hyperthyroidism occurring after hypopituitarism, on the other hand, is very rare. An extensive literature search revealed only six well-documented cases of hyperthyroidism in the presence of hypopituitarism. In two of these six cases, hyperthyroidism occurred after surgical hypophysectomy;[2,3] in one, after pituitary stalk section for malignant exophthalmos;[4] in two, after post-partum pituitary necrosis (Sheehan's syndrome);[5,6] and in one, after destruction of most of the pituitary by a chromophobe adenoma.[7]

Recently we treated a patient in whom hyperthyroidism developed in the presence of panhypopituitarism following deep x-ray therapy for a nasopharyngeal tumor invading the pituitary. Hyperthyroidism (Graves' type) appeared eight years after the documentation of panphypopituitarism. During the treatment of hyperthyroidism with radioiodine I-131, the patient experienced thyroid crisis. Three years after the I-131 treatment, primary hypothyroidism developed in addition to previously obscure pituitary thyroid-stimulating hormone (TSH) deficiency. In the management of this patient, a most unusual sequence of thyroid abnormalities occurred. The case is described in detail since it is the first of its kind to be reported.

From the Nuclear Medicine and Research Services, Veterans Administration Wadsworth Hospital Center, Los Angeles; and the Department of Medicine, University of California, Los Angeles, Center for the Health Sciences.

Submitted, revised, November 2, 1973.

Reprint requests to: G. T. Krishnamurthy, MB, MS, Nuclear Medicine Service, VA Wadsworth Hospital Center, Wilshire and Sawtelle Blvds., Los Angeles, CA 90073.

Admission History

In January 1961, a white man, 49 years old, with occasional epistaxis for six months, was suddenly stricken with diplopia. Three days later severe generalized headaches developed, the diplopia continuing. He was admitted to the Veterans Administration Wadsworth Hospital Center, Los Angeles. The previous history was not remarkable. On physical examination the patient was observed to be lethargic, with a poor memory, and an unsteady gait. The pupils were normal and the fundus had clear disc margins. He had bilateral complete abducens paralysis and unsustained nystagmus in both eyes on convergence. No abnormalities were noted in the remainder of the cranial-nerve and other nervous system examination. The blood pressure was 110/70 mm of mercury, the pulse rate 90 per min and regular. Results of cardiovascular respiratory system, and abdominal examination were within normal limits. The thyroid was not enlarged. Ear, nose, and throat examination disclosed an ulcerated lesion in the posterior nasal space in the left Rosenmuller's fossa. Blood cell counts and determinations of electrolytes and serum proteins were normal. Roentgenogram of the chest showed a normal heart and old inflammatory changes in the lungs. Laminograms of the skull and the sella turcica showed fullness of the posterior, nasopharyngeal region with erosion of the posterior clinoid process and the floor of the sella turica and sphenoid sinus.

Spinal fluid analysis showed protein content of 104 mg and sugar content of 52 mg per 100 ml, with no cells. Opening and closing pressure was normal. On perimetry examination the visual fields were normal. An electrocardiogram was

TABLE 1.—*Laboratory Investigations of Hyperthyroidism in the Presence of Panhypopituitarism (normal values in parentheses)*

		24-Hr Urine			*Plasma*				*Thyroid RAI Uptake*	
		17-KGS (5-20mg)	*17-KS (6-18mg)*	*Gonadotropin (5-40)*	*17-OHCS (7-25 μg per 100 ml)*	*PBI μgm (4-8)*	*T3 Resin Uptake (25-35%)*	*TSH μUnits (2-10)*	*6 hr (%) (5-25)*	*24 hr (%) (10-35)*
Before pituitary radiation										
1961	Baseline	8.3	19.3	>5-<40	3.6	6.5	53.0	..	8.0	13.0
	After Metyrapone	13.2	..	..	..	..	..	..	..	..
	After ACTH	..	..	..	17.7	..	..	..	..	..
After pituitary radiation										
1961*	Baseline	8.0	4.6	18.6	11.5	7.4	..	..	25.0	48.0
	After Metyrapone	9.3	13.1	..	20.2	..	..	..	..	..
	After ACTH	56.0	15.5	..	60.7	..	..	..	..	..
1968	On Dexamethasone	0.43	0.87	>5-<40	..	13.7	53.0	..	79.0	90.0
1971	On Dexamethasone	7.6	4.2	>5-<40	..	7.8	27.4	..	9.2	17.0
1972	Baseline	..	..	..	..	T4 by col 2.3 (2.9-6.4)	T3 Index 121 (Thyopac)	2.0	4.9	10.0
	After 20 units TSH	..	..	..	..	..	..	..	7.8	18.5

*4 months.

consistent with first-degree atrioventricular block and an old anterior and posterior myocardial infarction with T wave changes of recent ischemia.

A bilateral carotid angiogram was normal. Biopsy of the lesion in the posterior nasal wall was done twice, but the tissue did not show definite tumor cells.

It was felt that the patient had a tumor in the nasopharynx invading the pituitary, but because of his cardiac condition and the inaccessibility of the lesion, surgical operation was not contemplated. It was decided to treat him with deep x-ray therapy to the nasopharynx and the pituitary region.

The following baseline data were obtained: Protein-bound iodine 6.5 μg per 100 ml; six-hour and 24-hour thyroid radioiodine uptake, 8 and 13 percent, respectively; triiodothyronine resin uptake 53 percent; 24-hour urinary 17-ketogenic and 17 ketosteroid, 8.3 mg and 19.3 mg, respectively. Plasma cortisol at 8 a.m. was 3.6 μgm per 100 ml, rising to 17.7 μgm after 40 units of ACTH stimulation. The response to metyrapone (SU 4885) test was inadequate (Table 1).

The patient was treated with 4,055 rads of deep x-ray to the base of the skull and the pituitary fossa. He made an uneventful recovery and was discharged from the hospital after the full course of deep x-ray therapy.

Three months later, he was readmitted with a history of anorexia, nausea, weight loss of 35 pounds, and increased urinary output and thirst, with no recent decrease in libido.

Examination showed the blood pressure to be 90/60 mm and the pulse rate 88 per minute. The patient was thin and looked chronically ill. The skin was dry but no hyperpigmentation was found. Hair distribution was normal. The thyroid gland was not enlarged. No cardiovascular or respiratory systems abnormality was noted. The liver and spleen were not palpable, the testes were of average size, and the prostrate gland was normal. There was diffuse weakness, but no abnormal localizing neurological signs were found.

Laboratory data showed the following: blood cell counts and electrolyte content were normal, as were results of spinal fluid analysis; PBI was 7.4 μgm per 100 ml; thyroid radioiodine uptake at 6 hours and 24 hours was 25 and 48 percent, respectively; 24-hour urinary 17 ketosteroids and 17 ketogenic steroids were 4.6 mg and 8 mg per 100 ml, respectively, increasing to 15.5 mg and 56.0 mg after 40 units of ACTH stimulation. With metyrapone (SU 4885), 750 mg every six hours for 48 hours, the 24-hr urinary 17 ketogenic steroids increased only to 9.3 mg and 17 ketosteroids increased only to 13.1 mg per 100 ml. A diagnosis was made of adrenal insufficiency secondary to pituitary ACTH deficiency.

With 12 hours of water deprivation, the urinary specific gravity did not rise above 1.008. The patient lost 5 pounds of weight during the water-deprivation test and subsequently excreted 800 ml of urine in 8 hours. The test was discontinued when the patient became symptomatic. A diagnosis of diabetes insipidus was made. Urinary gonadotropin in a 24-hour specimen was 18.6 MU (Norm 10 to 40 MU). The patient continued

to be apathetic and anorectic, ran low blood pressure, and lost an additional 17 pounds while in the hospital. Subsequently he was given 0.5 mg of dexamethasone every 6 hours. He showed a remarkable recovery and gained 15 pounds in weight. He required no exogenous posterior pituitary extract, and was discharged receiving maintenance doses of dexamethasone.

Seven years later, in April 1968, the patient (then 56 years old) noticed increasing weight loss (35 pounds), sweating, heat intolerance, tremor, and diarrhea. Blood pressure was 144/74 mm of mercury, the body temperature 37°C (98.6°F) and the pulse 104 per min and irregular. The thyroid gland was enlarged, but no bruit was heard over it. A fine tremor was present in the hands, and the skin was smooth. The patient had a staring look and the eyes were protruding. The Hertel exophthalmometer reading was 21 mm in both eyes (normal less than 18 mm). There was no pretibial myxedema. On heart auscultation a grade II/VI ejection systolic pressure was heard at the base. The liver was palpable two fingerbreadths below the costal margin. The reflexes were hyperactive.

An electrocardiogram showed atrial fibrillation with evidence of old anterior and posterior myocardial infarction and biventricular enlargement. Twenty-four hour urinary 17 ketosteroids and 17 ketogenic steroids (the patient taking dexamethesone) were 0.87 mg and 0.4 mg, respectively. Urinary gonadotrophic levels were normal. PBI was 13.7 μg per 100 ml and radioactive iodine uptake was 79 percent at 6 hours and 90 percent at 24 hours. Triiodothyronine resin uptake was 53 percent (normal 25 to 35 percent). A scan showed the thyroid gland diffusely enlarged; the calculated weight was 53.4 grams.

A diagnosis of thyrotoxicosis was made. The patient was treated with 3.3 millicuries of radioactive iodine I-131 and was maintained on 10 mg of hydrocortisone three times daily.

Five days later, the patient became disoriented and confused. The temperature rose to 40°C (104°F), respirations 36 per minute, blood pressure 140/60 mm of mercury and the pulse 130 per min and irregular. The patient showed increasing signs of cardiac failure. An electrocardiogram indicated atrial fibrillation with fast ventricular response. Spinal fluid analysis at this time was within normal range and blood cultures were negative for pathogenic bacteria. A diagnosis of thyroid crisis was made. The patient was treated with digoxin, saturated solution of potassium iodide, propylthiouracil, propranolol, and ampicillin. Within 24 hours he showed remarkable improvement. Propylthiouracil, digoxin and hydrodiuril were continued. At the time of discharge, the PBI was 9.8 μg per 100 ml and triiodothyronine resin uptake was 36 percent. The symptoms of hyperthyroidism improved but did not disappear completely.

The patient was followed as an outpatient in the Endocrine and Nuclear Medicine Clinics. Symptoms of mild hyperthyroidism persisted. A year later, in 1969, shortness of breath, mild orthopnea, intermittent ankle edema, and increased nocturia developed. There was a notable loss of axillary and pubic hair. The patient showed all the signs of thyrotoxicosis: PBI was 15.9 μg per 100 ml, T3 resin uptake 43 percent, and 24-hour RAI uptake 63 percent. A scan showed diffuse enlargement of the thyroid gland with uniform I-131 distribution; the calculated weight of the gland was 49.2 grams. The patient was treated again, with 5 millicuries of I-131, and two weeks later with propylthiouracil. There was no evidence of exacerbation of thyrotoxicosis in the post-irradiation period. The patient improved and attained a completely euthyroid status six months following repetition of the radioactive iodine treatment. Propylthiouracil was discontinued. Digoxin and a diuretic agent and a maintenance dose of hydrocortisone were given.

Three years later, in 1972, the patient (then 60 years old) noticed a 15-pound increase in weight, lethargy, and cold intolerance. On examination, blood pressure was 130/80 mm of mercury and the pulse of 58 per minute and irregular. The skin was dry and rough, hair over the eyebrows and in the axillary and pubic regions was diminished, the thyroid gland was not palpable, and the reflexes were slow. Clinically, the patient appeared hypothyroid. Laboratory test results showed a T4 (by column) of 2.3 (normal 2.9 to 6.4) and a T3 resin index of 123 (more than 115 indicates hypothyroidism). Six-hour and 24-hour radioiodine uptake was 4.9 percent and 10.0 percent, respectively. After intramuscular injections of 10 units of bovine thyroid stimulating hormone (TSH) for two days, the radioiodine uptake rose only to 7.8 percent and 18.5 percent at 6 hours and 24 hours, respectively (a normal response is more than 20 percent at 24 hours). TSH by radioimmunoassay technique (Bio-Science) was 2 μ-units (an adult normal value is 2 to 10). These

tests established that the patient had both primary and secondary hypothyroidism due to radiation to the thyroid and the pituitary gland, respectively.

At the time of this report the patient was being managed with sodium levothyroxine (Synthroid®) 0.2 mg daily, digoxin 0.25 mg, hydrocortisone 20 mg and 10 mg (in the morning and afternoon, respectively), and diuretic agents.

Discussion

Panhypopituitarism

Panhypopituitarism is defined clinically as a deficiency of more than one pituitary hormone. There are two causes for panhypopituitarism in the patient reported upon herein. The first is direct invasion of the pituitary gland by nasopharyngeal tumor. A roentgenogram showed definite destruction of the pituitary fossa and the posterior clinoid process. Even though pre-radiation thyroid, adrenal, and gonadal functions were normal, partial destruction of the pituitary resulting from direct invasion by the tumor was indicated by inadequate response to the metyrapone test (Table 1). The second cause of panhypopituitarism in our patient is deep x-ray therapy given to the base of the skull in the vicinity of the pituitary.

Pituitary ACTH deficiency was documented within three months following deep x-ray therapy. Partial posterior pituitary deficiency of anti-diuretic hormone (ADH) was evidenced by a loss of urine concentration capacity when the patient was subjected to the water-deprivation test. There appears at present to be no severe damage to the ADH-producing center in the hypothalamus, for the patient has required no posterior pituitary replacement therapy during the last 11 years of follow-up.

The growth hormone is the pituitary hormone that most commonly shows deficiency during panhypopituitarism. This effect is usually followed by loss of gonadotropins, ACTH, and finally thyroid-stimulating hormone (TSH). Rabkin and Frantz, who studied 25 hypopituitary patients, have shown the frequency of hormonal loss to be: growth hormone, 100 percent; gonadotropins, 88 percent; adrenocorticotropic hormone, 56 percent, and thyroid-stimulating hormone, 52 percent.[8] They have also shown the extent of the disease as judged clinically to be far less than the hormonal deficit as measured by hormonal assay. Clinical manifestations of growth-hormone deficiency in adults are not definitely known. A reliable way of testing growth hormone reserve is by measuring the growth hormone response to insulin-induced hypoglycemia. Because of several problems in our patient, insulin-induced hypoglycemia test was not attempted.

Adrenal gland functions were tested both before and three months after deep x-ray therapy. Seventeen ketosteroids and 17 ketogenic steroid levels were normal before x-ray therapy. The response to ACTH stimulation was normal, but that to the metyrapone test was inadequate. Three months after x-ray therapy, the patient showed adrenal insufficiency secondary to pituitary ACTH insufficiency, as judged by an inadequate response to the metyrapone test and with an excellent response to the ACTH stimulation test. In one large series of patients, ACTH secretion was reported to be the last function to disappear in hypopituitarism.[9] In our patient, ACTH appeared to be the first to show deficiency (growth hormone response was not measured). In Rabkin and Frantz's series of 25 hypopituitary patients, ACTH deficiency ranked below growth hormone and gonadotropin and above TSH in frequency of loss. Isolated deficiency of ACTH is less common; seven cases had been reported up to 1964.[8]

Documentation of TSH deficiency was difficult when the patient was euthyroid, but the deficiency was easily evident when the patient became hypothyroid after treatment with I-131. Radioimmunoassayable TSH was only 2 μ-units when the patient was clearly hypothyroid, indicating deficiency of anterior pituitary TSH reserve. The question arises whether this low level of TSH was enough to maintain the patient in a euthyroid state for eight years when thyroid function was normal, or whether the thyroid gland was even then functioning autonomously. Even though TSH is essential for thyroid function, there are documented case reports in which patients were euthyroid in the absence of the anterior pituitary gland. Among ten of 350 patients with mammary cancer who remained euthyroid after hypophysectomy there was necropsy evidence in two that hypophysectomy had been complete, suggesting normal thyroid function in the absence of TSH.[1]

Isolated TSH deficiency is a rare entity. We were able to collect reports of only eight cases of well-documented isolated TSH deficiency in the literature up to 1964.[10-14] In our patient, TSH deficiency was associated with pituitary ACTH deficiency and normal levels of gonadotropins.

Hyperthyroidism

In the present case, thyrotoxicosis (Graves' disease) developed eight years after the documentation of panhypopituitarism. Graves' disease is characterized by some or all of the following five features: (1) diffuse goiter, (2) hyperthyroidism, (3) ophthalmopathy, (4) dermopathy (pretibial myxedema), and (5) long-acting thyroid stimulator (LATS) in the plasma. Our patient had three of the five—diffuse goiter, hyperthyroidism, and exophthalmos. There was no dermopathy and LATS was not measured. The pathogenesis of Graves' disease has been disputed for many years. It has been suggested that LATS is the cause of Graves' disease.[15,16] At present, there is controversy as to the role of LATS in Graves' disease, and many recent reports reject it as the cause.[17,18] In one reported case there was no hyperthyroidism when serum LATS titer was very high, but hyperthyroidism developed later when LATS titer decreased, lending support to the opinion that LATS is probably not the cause of the disease.[19]

In our patient, both hyperthyroidism and exophthalmos occurred after radiation of the pituitary. However, in two reported cases there was remission of Graves' disease following pituitary irradiation.[20,21] The authors of those reports claimed that Graves' disease was due to the excessive TSH produced by the pituitary, and the remission of the disease was attributed to pituitary ablation. The occurrence of Graves' disease in our patient after pituitary ablation seems to refute this hypothesis. Hyperthyroidism due to elevated TSH levels is rare. Until August 1972 there were only four reported cases of hyperthyroidism due to hypersecretion of TSH.[22] In our patient, hyperthyroidism was not due to TSH hypersecretion; indeed, TSH was low, presumably from the time of pituitary radiation.

Thyroid Crisis

It is difficult to distinguish where hyperthyroidism ends and thyroid crisis begins. Originally McArthur et al stated that thyroid crisis represents a state where hyperthyroidism is "life endangering."[23] There is general agreement at present that thyroid crisis represents hyperthyroidism complicated by rapid onset of pronounced tachycardia, tachypnea, and signs of central nervous system, hepatic, and gastrointestinal dysfunction. During crisis, thermoregulatory and psychic dysfunction predominate among central nervous system effects. Diarrhea and hyperbilirubinemia are also occasionally seen.

Thyroid crisis is of either medical or surgical origin. Surgical crisis occurs postoperatively, after operation for hyperthyroidism. The cause of medical thyroid crisis is mostly iodiopathic. There are, however, three well-defined precipitating factors: (1) infection, trauma, or mental stress; (2) discontinuation of thyrostatic medication; and (3) radioiodine therapy. Lamberg, in Finland, reported 17 medical thyroid crisis cases between 1955 and 1958.[24] In these cases trauma and infection were the predominant causes. Nelson and Becker reported 21 instances of thyroid crisis among 2,329 patients admitted to the hospital for thyroid problems between 1949 and 1967.[25] A total of 625 patients were treated surgically. Only two among the 21 thyroid crises occurred after operation. In their study also, infection was the most common precipitating factor.

Thyroid crisis following radioiodine treatment has been reported in a few instances.[26] The crisis usually occurs four to ten days after radioiodine treatment. In our patient, thyroid crisis developed five days after radioiodine treatment, manifesting disorientation, pyrexia (40°C, 104°F), tachypnea, tachycardia, and cardiac failure. There was no diarrhea or hyperbilirubinemia.

The treatment of thyroid crisis is challenging. Mortality can be high if the crisis is not treated adequately. In Nelson and Becker's series of 21 patients with thyroid crisis, only five survived.[25] The high mortality was attributed to the advanced age of the patients. In contrast, all seven patients with thyroid crisis treated with reserpine by Dillon et al survived.[27]

The crisis following radioiodine treatment is not related either to the size of the thyroid gland or to the dose of radioiodine given. There appears to be a correlation with toxic nodular goiter. Lamberg et al reported that in six out of seven patients with toxic nodular goiter, crisis developed after radioiodine treatment.[28] Thus it appears that caution should be exercised, especially in treating toxic nodular goiter with radioiodine.

Low TSH levels in the presence of hypothyroidism indicate secondary (pituitary) hypothyroidism. The availability of synthetic thyrotropin-releasing-hormone (TRH) stimulation tests enables one to distinguish pituitary from hypothalamic hypothyroidism.[29] The evidence gathered on our patient indicates that the secondary hypothyroidism is of pituitary origin.

Primary Hypothyroidism

At present, because it is so widely used, radioiodine treatment for hyperthyroidism is the most common cause of primary hypothyroidism. In a 20-year follow-up study at the Veterans Administration Wadsworth Hospital Center, the mean incidence of hypothyroidism for 241 men with Graves' disease who were treated with I-131 was 27.8 percent.[30] Only 10.4 percent during the first year, and 21.2 percent during the first five-year period, became hypothyroid. Our patient, who had received a total of 8.3 millicuries of radioiodine, became hypothyroid within three years after the second dose. What part the lack of adequate TSH stimulation played in the genesis of primary hypothyroidism in our patient is difficult to establish.

The diagnosis of primary hypothyroidism requires the presence of inadequate response by the thyroid to TSH stimulation and an increase in endogenous serum TSH levels. In our patient, only one of two criteria, lack of response to TSH stimulation, can be used as evidence of primary hypothyroidism. After 10 units of TSH for two days, radioiodine uptake rose from a pre-TSH level of 4.9 percent at 6 hours and 10.0 percent at 24 hours to a post-TSH level of 7.8 percent at 6 hours and 18.5 percent at 24 hours, respectively. In three patients with pituitary hypothyroidism reported by Lohrenz et al, the post-TSH thyroid uptake rose to three to seven times the pre-TSH level.[10] In our patient, the post-TSH level was less than twice the pre-TSH level. Such low post-TSH responses are reported only in hypothyroidism due to Sheehan's syndrome, whereas other types of anterior pituitary lesions have shown a greater response to TSH.[31] Thus, in our patient, primary and secondary hypothyroidism were caused by radiation to the thyroid and to the pituitary gland, respectively. In an extensive search of the literature no other case of this kind was found.

Summary

Hyperthyroidism developed in a patient eight years after the onset of panhypopituitarism following deep x-ray therapy to a nasopharyngeal tumor invading the pituitary. The patient experienced thyroid crisis five days after radioactive iodine therapy for hyperthyroidism; and, three years later, primary hypothyroidism developed in addition to previously obscure pituitary TSH deficiency. This is believed to be the first such case reported. In the management of this patient, a most unusual sequence of endocrine abnormalities occurred.

REFERENCES

1. Pazianos AG, Benua R, Ray BS, et al: Persistent thyroid function following hypophysectomy. J Clin Endocr 20:1051-1058, 1960

2. Christensen LK, Binder V: A case of hyperthyroidism developed in spite of previous hypophysectomy. Acta Med Scand 172:285-288, 1962

3. Gurling KJ, Baron DN, Smith EJR: Thyroid adenomas and thyrotoxicosis in patients with hypopituitarism following hypophysectomy. J Clin Endocr 19:717-725, 1959

4. McCullagh EP, Reynolds CW, McKenzie JM: Hyperthyroidism after section of the pituitary stalk for malignant exophthalmos—Report of a case. J Clin Endocr 20:1029-1033, 1960

5. Irvine WJ, Cullen DR, Kirkham KI, et al: Sheehan's syndrome associated with thyrotoxicosis and diabetes mellitus. Proc Roy Soc 62:40, 1969

6. Fajans SS: Hyperthyroidism in a patient with postpartum necrosis of the pituitary: Case report and implications. J Clin Endocr 18:271-277, 1958

7. Werner SC, Stewart WB: Hyperthyroidism in a patient with a pituitary chromophobe adenoma and a fragment of normal pituitary. J Clin Endocr 18:266-270, 1958

8. Rabkin MT, Frantz AG: Hypopituitarism: A study of growth hormone and other endocrine functions. Ann Intern Med 64:1197-1207, 1966

9. Hokfelt B, Luft R: The effect of supracellar tumours on the regulation of adrenocortical function. Acta Endocr (Kobenhaven) 32:177-186, 1959

10. Lohrenz FN, Fernandez R, Doe RP: Isolated thyrotropin deficiency: Review and report of three cases. Ann Intern Med 60: 990-998, 1964

11. Shuman CR: Hypothyroidism due to thyrotropin deficiency without other manifestations of hypopituitarism. J Clin Endocr 13: 795-800, 1953

12. Sampson MC, Rose E, Herbert E: Solitary ("Monotropic") thyrotropin deficiency with secondary hypothyroidism: Observations on response to thyrotropin, growth hormone and sodium l-thyroxin. Am J Med 17:871-879, 1954

13. Lins H, Zimmerman H: Diagnose und Therapie der Hypolhysären schilddrüsenunterfunktion. Zschr Klin Med 156:87-93, 1959

14. Morandi L, Clemencon G, Amstein H: Die Klinischen formen der hypophysenvorder lappen insuffizienz. Schweiz Med Wschr 87:867-873, 1957

15. Adams DD, Purves HD: Abnormal responses in the assay of thyrotropin. Proc Univ Otago Med Sch 34:11-12, 1956

16. Adams DD: Pathogenesis of the hyperthyroidism of Graves's disease. Br Med J 1:1015-1019, 1965

17. Chopra IJ, Solomon DH, Johnson DE, et al. The thyroid gland in Graves' disease: Victim or culprit? Metabolism 19:760-772, 1970

18. Silverstein GE, Burke G: Thyroid suppressibility and long-acting thyroid stimulator in thyrotoxicosis. Arch Intern Med 126: 615-620, 1970

19. Chopra IJ, Solomon HD: Graves' disease with delayed hyperthyroidism. Onset after several years of euthyroid ophthalmopathy, dermopathy, and high serum LATS. Ann Intern Med 73:895-990, 1970

20. Hermann K: Pituitary exophthalmos; assessment of methods of treatment. Br J Ophth 36:1-19, 1952

21. Jailer JW, Holub DA: Remission of Graves' disease following radiotherapy of a pituitary neoplasm. Am J Med 28:497-500, 1960

22. Emerson CH, Utiger RI: Hyperthyroidism and excessive thyrotropin section. N Engl J Med 287:328-333, 1972

23. McArthur JW, Rawson RW, Means JH, et al: Thyrotoxic crisis—Analysis of 36 cases seen at Massachusetts General Hospital. JAMA 134:868-874, 1947

24. Lamberg BA: The medical thyroid crisis. Acta Med Scand 164:479-496, 1959

25. Nelson NC, Becker WF: Thyroid crisis: Diagnosis and treatment. Ann Surg 170:263-273, 1969

26. Shafer RB, Nuttall FQ: Thyroid crisis induced by radioactive iodine. J Nucl Med 12:262-264, 1971

27. Dillon PT, Babe J, Meloni CR, et al: Reserpine in thyrotoxic crisis. N Engl J Med 283:1020-1023, 1970

28. Lamberg BA, Hernberg CA, Wahlberg P, et al: Treatment of toxic nodular goitre with radioactive iodine. Acta Med Scand 165:245-258, 1959

29. Pittman JA Jr, Haigler ED Jr, Hershman JM, et al: Hypothalamic hypothyroidism. N Engl J Med 285:844-845, 1971

30. Blahd WH, Hays MT: Graves' disease in the male: A review of 241 cases treated with an individually calculated dose of sodium iodide I-131. Arch Intern Med 129:33-40, 1972

31. Taunton OD, McDaniel HG, Pittman JA Jr: Standardization of TSH testing. J Clin Endocr 25:266-277, 1965

Refer to: Epstein E: Treatment of a cutaneous nocardia asteroides infection with minocycline hydrochloride. West J Med 120:497-499, Jun 1974

Treatment of a Cutaneous Nocardia Asteroides Infection with Minocycline Hydrochloride

ERVIN EPSTEIN, MD, *Oakland*

COMPROMISED HOST DEFENSE MECHANISMS caused by a disease-altered immunological system may provide the setting for nocardial infection. Man probably has a significant natural immunity to this fungus, as manifest by the few cases of disease despite the ubiquity of the organism in nature. Once active infection has occurred, however, disease is often progressive and resistant to treatment. It appears more prominently in present-day infections because many patients with diseases previously considered fatal are now being maintained by complex or long-term immunosuppressive chemotherapy. These persons, whose diseases have predisposed them to secondary invaders, can readily acquire an infection caused by Nocardia asteroides.[1,6,10,12,13]

The diagnosis can be difficult. Unless it is suspected, there is a tendency to overlook the organism. Usually the lungs are the site of infection, but other organs—the skin, for example—may be involved either by dissemination or by direct primary infection.[7,9,11] Murray and his coworkers[9] studied the prevalence of nocardial infections up to 1960 and found that 31 percent were exclusively in the respiratory tract and 14.5 percent exclusively in the skin and subcutaneous tissues. In reviewing the literature, Bianco and his coworkers[4] cited one report stating that primary pulmonary nocardiosis occurred in 60 percent of cases through 1949, and a second report, dated five years later, stating that pulmonary involvement occurred in 65 percent of the cases, subcutaneous involvement in 34 percent, and central nervous system involvement in 24 percent. Whatever the site of infection, bacteriological testing of cultures will reveal the nocardia at times only if they are incubated longer than usual (from 3 to 10 days).[1,12]

To be successful, therapy must be aggressive even to the point of extending treatment for several months to a year beyond clinical cure.[11,12] Although sulfonamides have been the classic agents for treating nocardial infections, it is now becoming apparent that other antibacterial agents are efficacious. Recently, Castleman and his associates[5] discussed an opportunistic pulmonary Nocardia asteroides infection in a 71-year-old man undergoing treatment with a cytotoxic agent and a corticosteroid for reticulum-cell sarcoma. Following ten days of ineffectual sulfisoxazole therapy, the patient responded: The lung lesion decreased in size after just 3 days of minocycline therapy. Bach and his associates[2] reported that minocycline was used with success to treat nocardiosis in a renal-transplant patient.

Minocycline (Minocin,® Lederle), a new member of the tetracyclines, is a broad-spectrum antibiotic with effectiveness against a wide variety of microorganisms which are sensitive to, and in some instances resistant to, other tetracyclines. It is absorbed rapidly and almost completely from the gastrointestinal tract after oral administration. Serum levels peak within 2 to 3 hours, and therapeutic concentrations are maintained on a 100 mg twice-daily dosage schedule. Like other tetracyclines, minocycline is thought to act by interfering with nucleic acid metabolism and protein synthesis of microorganisms.

Two recent *in vitro* studies are illustrative of the activity of minocycline against N. asteroides isolates. In the first, Bach and coworkers[3] tested 35 isolates of N. asteroides against most of the antimicrobials now available. Minocycline proved to be the most active: 90 percent of the isolates tested were inhibited by 3.1 μg per ml or less, and all were inhibited by 6.3 μg per ml or less.[3] In the second study, Lerner and Baum[8] designed a new suitable assay system for nocardia species and tested it with 30 strains of N. asteroides against 31 antimicrobial agents. They reported the newer

From the Department of Dermatology, University of California, School of Medicine, San Francisco.

Submitted October 10, 1973.

Reprint requests to: E. Epstein, MD, 400 - 30th Street, Oakland, CA 94609.

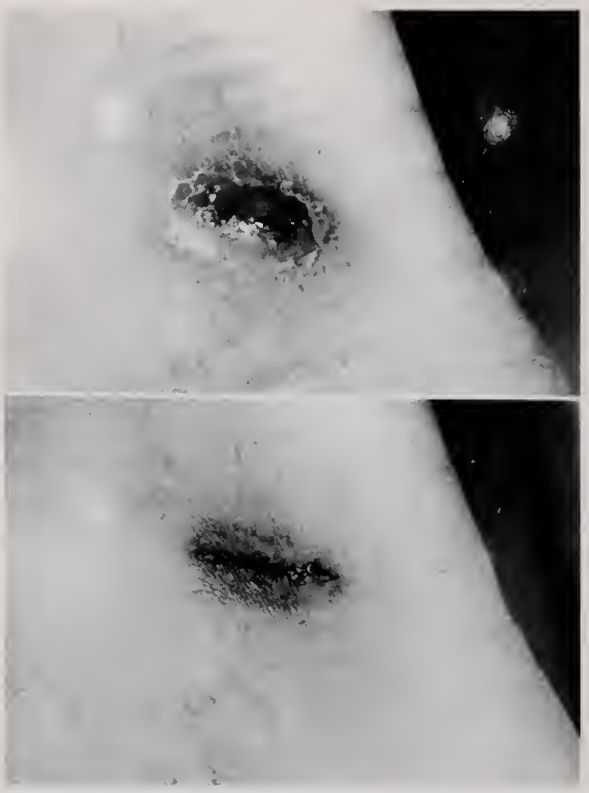


Figure 1.—In upper picture, lesion on ankle infected with nocardia asteroides shows continuing cellulitis after six weeks of therapy with minocycline. After four more weeks of treatment with minocycline the lesion (lower picture) was almost completely healed.

agents to be especially active: minocycline at concentrations of 3.1 μg per ml or less inhibited 95 percent of the isolates.

In clinical usage the main adverse reactions encountered during minocycline administration are those usually associated with tetracyclines: gastrointestinal effects, such as nausea and vomiting. Occasionally lightheadedness or dizziness occurs but may disappear during therapy and definitely does disappear when the drug is discontinued.

The following case report illustrates the clinical effectiveness of minocycline against a nocardial infection.

Report of a Case

A 68-year-old-man with a long-standing history of leukemia and psoriasis requested an examination of a large pustule on the left ankle which had been present for approximately one month. It was observed to be an indurated draining abscess with a surrounding area of cellulitis. A culture was taken. There was no evidence of nocardial involvement of any system other than the cutaneous. Minocycline therapy was begun at the recommended dose of 200 mg (2 capsules) initially followed by 100 mg (1 capsule) every 12 hours.

The bacteriological report indicated a large fungal growth which proved to be Nocardia asteroides as well as a scant growth of Staphylococcus epidermidis. Disc sensitivity testing of the N. asteroides showed it to be resistant to ampicillin, gentamicin, kanamycin, lincomycin, methicillin, and streptomycin; intermediately resistant to chloramphenicol, erythromycin, and penicillin; and sensitive to cephalothin, tetracycline, and minocycline.

After one week of therapy the ankle appeared somewhat improved. Five weeks later, it was considerably better. A photograph taken at this time showed continuing cellulitis (Figure 1). An additional four weeks of minocycline therapy resulted in complete healing of the ankle infection. A final photograph taken two weeks later shows the ankle to be well healed. At this time no evidence of disseminated nocardia in other organ systems could be found. The most recent chest roentgenogram is normal, and central nervous system function is also normal. Laboratory examinations showed the last blood cell count and serum electrophoresis to be within normal limits, and the serum protein to be 5.9 grams per 100 ml. Throughout the 77 days of therapy, the patient experienced no adverse effects.

Discussion

Altered host defenses may predispose a person to the initiation of infections caused by opportunistic organisms. The patient described herein had two chronic diseases, psoriasis and leukemia. He had been taking chlorambucil (Leukeran®), 2 to 6 mg daily to control the leukemia, for two years before the onset of the nocardial infection. It is probable that the lowered body resistance permitted the nocardia organism to gain a foothold. Extended therapy with minocycline (200 mg initially, followed by 100 mg twice daily) brought about a clinical cure.

Summary

A patient with psoriasis and leukemia was examined because a large pustule had developed on his left ankle. Bacteriological cultures showed the presence of Nocardia asteroides. The infection

was successfully treated with minocycline administered at the recommended dosage for 77 days and there was no adverse reaction.

REFERENCES

1. Adams AR, Jackson JM, Scopa J, et al: Nocardiosis: Diagnosis and management, with a report of three cases. Med J Aust 1:669-674, Mar 1971

2. Bach MC, Monaco AP, Finland M: Pulmonary nocardiosis—Therapy with minocycline and with erythromycin plus ampicillin. JAMA 224:1378-1381, Jun 1973

3. Bach MC, Sabath LD, Finland M: Susceptibility of Nocardia asteroides to 45 antimicrobial agents in vitro. Antimicrob Agents Chemother 3:1-8, Jan 1973

4. Bianco AJ, Johnson EW, Martin WJ, et al: Nocardiosis without involvement of the pulmonary or central nervous system. Proc Staff Meetings Mayo Clinic 32:119-123, Mar 1957

5. Castleman B, Scully RE, McNeely BU: Case records of the Massachusetts General Hospital, case 21-1973. N Engl J Med 288:1115-1121, May 1973

6. Cross RM, Binford CH: Infections by fungi that are commonly primary pathogens. Is Nocardia asteroides an opportunist? Lab Invest 11:1103-1109, Nov 1962

7. Goodman JS, Koenig MG: Nocardia infections in a general hospital. Ann NY Acad Sci 174:552-567, Oct 1970

8. Lerner PI, Baum GL: Antimicrobial susceptibility of nocardia species. Antimicrob Agents Chemother 4:85-93, Aug 1973

9. Murray JF, Finegold SM, Froman S, et al: The changing spectrum of nocardiosis—A review and presentation of nine cases. Ann Rev Respir Dis 83:315-330, Mar 1961

10. Neu HC: Diagnosis and treatment of five opportunistic infections. Med Times 100:77-85, Mar 1972

11. Peabody JW, Jr, Seabury JH: Actinomycosis and nocardiosis—A review of basic differences in therapy. Am J Med 28:107-115, Jan 1960

12. Saltzman HA, Chick EW, Conant NF: Nocardiosis as a complication of other diseases. Lab Invest 11:1110-1117, Nov 1962

13. Young LS, Armstrong D, Blevins A, et al: Nocardia asteroides infection complicating neoplastic disease. Am J Med 50: 356-367, Mar 1971

LETTERS *to the Editor*

Verminous Ophthalmia

To the Editor: The appearance of live worms in the cul-de-sac of people in the United States is not common. There are reports and literature concerning it, however, particularly in the west. This concerns a case where the live worms were picked up from the slit lamp examination in the office with an ultimate diagnosis that they were thelaziasis Californiensis. The importance of the report is the appearance of the face fly, which is a newcomer and bears the name of Musca autumnalis, which may increase the incidence of this problem.[1]

The worms had the appearance of a short lively piece of nylon fishing line about 10 mm long. There are reports of corneal scarring, but none was seen in this case. The potential for penetration into the host is known to exist, but ordinarily this has not occurred with this particular type of worm. The wild animals of the Sierra foothills are the host with flies being the vector. The treatment was simply to lift them mechanically from the eye.

Duke Elder reports that cocaine will poison the fly locally, eliminating the problem.[2] Thiabendazole 4 percent locally can be tried. Oral usage of the same medication may be a possibility. In this particular case they were not of great value when tried. Since the patient did not continue to return with more worms, thiabendazole has not been used. No pocket from which the worms appeared or into which they disappeared could be found anywhere, implying that these worms, which were immature, were residing loose or free in the conjunctival sac without penetrating into the subconjunctival or body host tissues.

Karl J. Chiapella, MD
Chico, California

REFERENCES

1. California Department of Public Health (Personal Communication)
2. Duke Elder—System of Ophthalmology, Vol VIII, 1965, p 416

On the Performance of Electromyography (EMG)

To the Editor: Although the problem has not been acute on the West Coast until recently, there is a growing shortage of physicians trained to do EMGs and this shortage is becoming more acute. For instance at Rancho Los Amigos Hospital it has been difficult for several years to get any more than a small number of EMGs performed and the waiting period is long. In many instances, at this hospital, desired EMGs are not being performed at all.

Because of this shortage throughout the country, some physical therapists have become proficient in performing EMGs and they are providing this service. These EMGs are only performed upon referral from a physician.

A physical therapist is particularly appropriate to do this type of examination because of his strong background in anatomy and particularly in functional anatomy which in actual fact often surpasses many modern trained physicians. With special training this therapist's background is even more suitable. Throughout this recommendation it is the understanding that only those physical therapists particularly well trained and supervised by physicians knowledgeable in this technique would be used to perform these tests.

It should be noted that the United States Army and their centers and the United States Public Health Service Hospitals use specially trained physical therapists to perform EMGs. An orthopedic surgeon at Loma Linda University Medical Center used specially trained physical therapists for EMGs when he was in the Service and he states that their quality of work was exemplary.

It is common knowledge that a physician in a medical center in New York has three physical therapists doing EMGs in his department. It is further knowledge that a physical therapist has been doing EMGs in a county facility in California for several years.

Because some physical therapists in California have been doing nothing but EMGs for several years, any regulations that might inhibit them

from performing their tasks, could appropriately be challenged in the courts.

To put the subject of EMGs in proper perspective, we should realize that the trend today is to train the Allied Health professionals so they can be utilized in areas that were once thought to be the domain solely of the physician. An example of this is the Cardiac Care Unit where life threatening and emergency situations exist. Nowhere else could we think of an example of Allied Health personnel performing professional tasks under critical situations in a most proficient manner as exemplified by a decrease in the mortality by their efforts.

Jacquelin Perry, MD, one of the leading authoriteis in kinesiology, in a personal letter wrote, "The anatomy is well established and readily learned. Superficial muscles are generally the ones sampled because of convenience and patient comfort, and because these have the same innervation patterns as the deeper muscles. Vital neurovascular structures are readily avoided by anatomical consistency and protected by fascial planes and muscle arrangement.

"It is appropriate that diagnostic interpretations be reserved for physicians who will place the EMG findings in perspective with other clinical characteristics of the patient. However, techniques of obtaining the data and interpreting the signals are logical functions for a well trained physical therapist."

Many of our associates agree with Charles Engh, MD, of Arlington, Virginia who wrote, "Physical therapists with specialized training in electromyography should not be unfairly prevented from using this technique. I don't mean to imply that every physical therapist should carry out electromyographic study. It is, however, narrow minded to assume that only licensed physicians and surgeons are intelligent enough to derive useful information from this type of examination."

In our opinion it is ethical and legal to develop a program to appropriately train physical therapists in the skills of EMG to be performed under the supervision of a physician as outlined in Resolution No. 52 at the American Medical Association convention in Anaheim.

VERNON L. NICKEL, MD
Chairman, Department of Orthopedic Surgery and Rehabilitation

EDD J. ASHLEY, RPT, MPH, ED D
Coordinator, Rehabilitation Services
Loma Linda University Medical Center

Bran Revisited

TO THE EDITOR: In a recent article Dr. Alex Shulman [Shulman AG: High bulk diet for diverticular disease of the colon. West J Med 120:278-281, Apr 1974] mentioned that some "leading authorities" have suggested that bran should be added to the American diet on a trial basis. This letter is being written with the hope that we may not unnecessarily add another to the list of iatrogenic diseases.

In 1926, when I was a medical student, a San Francisco gastroenterologist spent one hour per week lecturing to us. One of his statements I remember: "Over 50 percent of my practice is a result of the present craze for eating bran." (At that time food faddists were promoting bran in much the same way that they now promote "natural foods.")

During forty-odd years of private practice I have seen several children with chronic adominal pain whose cramps have been relieved by discontinuing the use of breakfast cereal containing bran.

There is probably a segment of our population who can tolerate the daily ingestion of bran, but there is another segment who cannot. There is no good reason for adding an irritating substance like bran to the diet as long as there are plenty of other bulk-producing foods.

LUCAS W. EMPEY, MD
Sacramento

Trauma Rounds

Chief Discussant
F. WILLIAM BLAISDELL, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is the fourth of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Blaisdell FW: Indications for laparotomy following blunt abdominal injury (Trauma Rounds). West J Med 120:502-506, Jun 1974

Indications for Laparotomy Following Blunt Abdominal Injury

JOHN YOUNG, MD:* *Our patient today is one who was injured by blunt trauma to the abdomen. The case will be presented by Dr. Mark Winchester.*

MARK WINCHESTER:† The patient is a 22-year-old causasian man who while a passenger was in a motor vehicle accident approximately an hour before he was admitted to San Francisco General Hospital. At the time of entry he complained of generalized abdominal pain and pain over the left knee. He denied shoulder pain and the remainder of the history was not remarkable.

The patient was alert and in acute discomfort. The blood pressure was 120/70 mm of mercury, the pulse rate 80, and respiration 24 per minute and shallow. The skin was of good color and the extremities were warm. No abnormalities were noted in the head, eyes, ears, nose, or throat. The patient could take a deep breath without discomfort. There was no rib tenderness. The abdomen was flat to slightly distended, and the muscles were relaxed. There was suggestion of diffuse tenderness which was most evident in the left upper quadrant. There was question as to rebound tenderness. Peristalsis was active. There were abrasions over both knees and tenderness over the left patella.

The hematocrit was 40 percent, and leukocytes numbered 18,000 with the cell differential showing a shift to the left. The urine was clear both on gross and microscopic examination. No abnormality was noted on an x-ray film of the chest. An abdominal film showed a probable compression fracture of the fourth lumbar vertebra but was not otherwise remarkable.

During the next hour and a half of observation, the patient's condition was stable. The abdominal findings did not change appreciably. A repeat hematocrit was 41 percent. Peritoneal irrigation was carried out and as the catheter passed into the peritoneal cavity, gross blood returned. The patient was taken immediately to the operating room, 3 hours after injury and 2 hours after admission to hospital.

DR. YOUNG: *Doctor Blaisdell, would you comment on the abdominal evaluation?*

F. WILLIAM BLAISDELL, MD:‡ The most difficult type of traumatic injury that we are called on to evaluate as general surgeons is the blunt abdominal injury. The degree of violence is difficult to assess, and the abdominal findings may be negligible in the face of catastrophic injury. With the exception of rupture of the full bladder and the

*Chief Resident, Trauma Service.

†4th Year Medical Student, University of California, San Francisco.

Supported in part by NIH Grant GM 18470 and the Northern California Trauma Committee, American College of Surgeons.

Reprint requests to: D. D. Trunkey, MD, University of California Service, San Francisco General Hospital, San Francisco, CA 94110.

‡Chief of Surgical Service, San Francisco General Hospital; Professor of Surgery, University of California, San Francisco, School of Medicine.

very rare intestinal injury, for all practical purposes it is the solid organs that are injured by blunt trauma. Since the primary immediate complication of injury to a solid viscus is bleeding, the evaluation of blunt abdominal injury settles down to an evaluation of possible intraperitoneal bleeding.

The clues in the present case which suggest the possibility of intra-abdominal injury are slight distension and tenderness of the abdomen. It is stated that the hematocrit was normal and that the skin of the extremities was warm. This suggests that if there is intraperitoneal bleeding, the blood loss must be negligible, probably less than 500 ml. Blood loss in excess of this amount usually produces a detectable degree of peripheral vascular spasm. It requires 3 or 4 hours for the hematocrit to stabilize and reflect the degree of hemorrhage, so the normal hematocrit would not rule out the possibility of intraperitoneal bleeding.

The best screening test that I know for rib fractures is a deep inspiration. Since this patient could take a deep breath without difficulty, the likelihood of rib fracture was small. This, combined with the comment that there was no tenderness over the ribs, suggests that there was no injury to the chest wall. The reason this is important is that injuries to the liver and the spleen are often associated with rib fractures. If ribs 8, 9 or 10 are fractured, on the left side of the abdomen for example, in one case in five there is associated rupture of the spleen. Kehr's sign may be positive when there is blood under the diaphragm. This is because the central tendon of the diaphragm is innervated by the fifth cervical nerve, the same nerve that supplies sensation to the shoulder. Therefore, the absence of shoulder pain in this patient was a significant negative.

The absence of blood in the urine does not rule out urinary tract injury but makes it less likely.

Doctor Young, was an intravenous pyelogram considered in this case?

Dr. Young: We did consider an intravenous pyleogram but the nature of the injury, the absence of flank tenderness, and the fact that the urine was normal suggested that urinary tract damage was most unlikely. We settled for a plain film of the abdomen.

Dr. Blaisdell: In summary thus far, the evidence does not suggest a significant amount of intraperitoneal hemorrhage from injury to the liver, spleen or kidney. Bladder rupture seems most unlikely and a pancreatic or mesenteric or bowel injury even less so. The reason I have ignored the positive peritoneal aspirate is that, as you will see in a few minutes, I plan to take issue with this examination.

Another positive item in the findings reported to us was the elevated leukocyte count—18,000 per cu mm. I saved this abnormality for last, for I feel this is a very significant finding in this particular case. During the period of 2 hours of observation, the patient did not manifest much evidence of blood loss. The hematocrit actually rose from 40 to 41 percent. If there had been major intraperitoneal hemorrhage, there should have been clinical signs of shock and the hematocrit should have fallen at least 2 or 3 points in the two and a half hours between the accident and the last hematocrit. When intraperitoneal hemorrhage is minimal the only manifestation may be an elevation of the leukocyte count. This is particularly true of blood loss between 100 and 500 ml. In the absence of overt injury elsewhere and the suggestion that things were not quite right in the abdomen, this otherwise unexplained increase in leukocyte count becomes very significant. It might not in itself be an indication for a laparotomy but it should lead to careful observation of the patient and a high index of suspicion. If in the subsequent 4 to 6 hours there are increasing abdominal signs, a progressive fall in the hematocrit, the development of postural hypotension or peripheral vasoconstriction, continuing blood loss is established. This should lead to the conclusion that intraperitoneal hemorrhage is present and laparotomy is indicated.

With regard to the peritoneal irrigation which was carried out, I question the indication for this procedure. Certainly in this case the positive peritoneal paracentesis led to prompt laparotomy, but the procedure is not without iatrogenic hazard, for introduction of the catheter could cause bleeding. In somewhere between 3 and 5 percent of our cases in which peritoneal irrigation is carried out, complications are induced which necessitate laparotomy.

I would reserve peritoneal catheterization for a specific group of cases. Peritoneal irrigation is of greatest value in patients with multiple injuries. If the patient has some other associated injury such as a fractured femur, which also produces blood loss, assessment of vital signs and hematocrit are of little value. Under these circumstances

and in a case such as the one under discussion, peritoneal irrigation might be helpful. The procedure also may be useful if the patient has multiple rib fractures. In these circumstances, abdominal spasm may well be present due to the rib injury alone and the abdomen may be difficult to assess. As we have indicated, when there are fractures of the lower ribs on either the right or left, the possibility of liver or spleen rupture must be considered and peritoneal irrigation may be of value. If the patient has a depressed level of consciousness from head injury, drugs or alcohol, the abdominal evaluation may be difficult and sampling peritoneal fluid may be of value.

DONALD D. TRUNKEY, MD:* *Would you describe the technique of peritoneal irrigation that you used?*

DR. YOUNG: We used the kind of catheter that renologists use for peritoneal irrigation in renal failure. It is a soft, plastic tube 4 mm in diameter with multiple fenestrations and a sharp, central, metal stylet. The technique is as follows: First the bladder must be empty. This can be assured by placing an indwelling Foley catheter beforehand or by having the patient void just before insertion of the catheter. The optimal site for insertion is the abdominal midline just below the umbilicus (Figure 1). The skin is infiltrated with 1 percent xylocaine. The infiltration is carried straight down through the fascia and a small amount is placed at the level of the peritoneum. The skin is incised with a No. 11 blade for a distance of approximately 1 cm. Then, in a normally nourished patient, blunt dissection can be carried down through the subcutaneous fat so that a 2 or 3 mm niche can be placed in the midline of the fascia. This lessens resistance to advance of the catheter through the abdominal wall. To prevent sudden thrust of the catheter as the resistance of the abdominal wall is overcome, steady pressure on it is maintained by using one hand to press the stylet forward while the other hand exercises a retarding force. Once the resistance of the abdominal wall is passed, the stylet is removed and the catheter is advanced slowly past the fenestrations and taped in place.

The immediate return of gross blood indicates intraperitoneal hemorrhage and the test is considered positive. In most instances, no blood is encountered and 1,000 ml of Ringer's lactate is allowed to run in the peritoneal cavity over a period of 5 to 10 minutes. The seal on the bottle is then broken by the insertion of a No. 18 needle through the top of the intravenous bottle, the bottle is placed on the floor and the peritoneal cavity is drained (Figure 2). When there is good irrigation, usually 500 to 700 ml of fluid returns from the peritoneal cavity over the first 10 or 15 minutes. The presence of a light salmon color is equivocally positive. A deep pink is considered positive for hemorrhage. The presence of turbid or cloudy fluid is tentatively positive for inflammation. Some of the material is sent for determination of amylase content and the remainder is put into a counting chamber for leukocyte count. A count above 2,000 per cu mm is considered positive and suggests intraperitoneal inflammation or perforation of a hollow viscus.

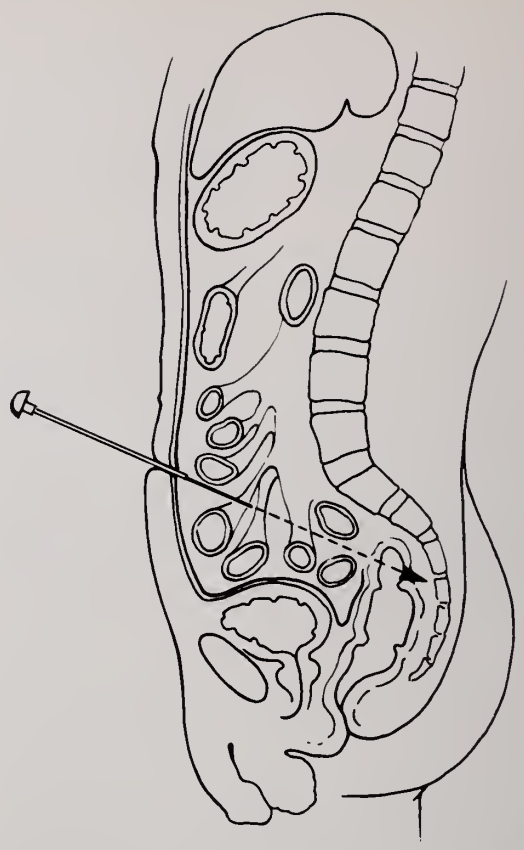


Figure 1.—Direction of insertion of stylet for abdominal paracentesis. (From Dunphy JE, Way LW: Current Surgical Diagnosis and Treatment. Los Altos, CA, Lange Medical Publications, 1973.)

If the returning fluid contains blood but progressively clears as it drains, this suggests that the bleeding was caused by the catheter tip whereas if the fluid remains uniform in color or

*Chief of Surgery, Emergency Service, San Francisco General Hospital; Assistant Professor of Surgery, University of California, San Francisco, School of Medicine.

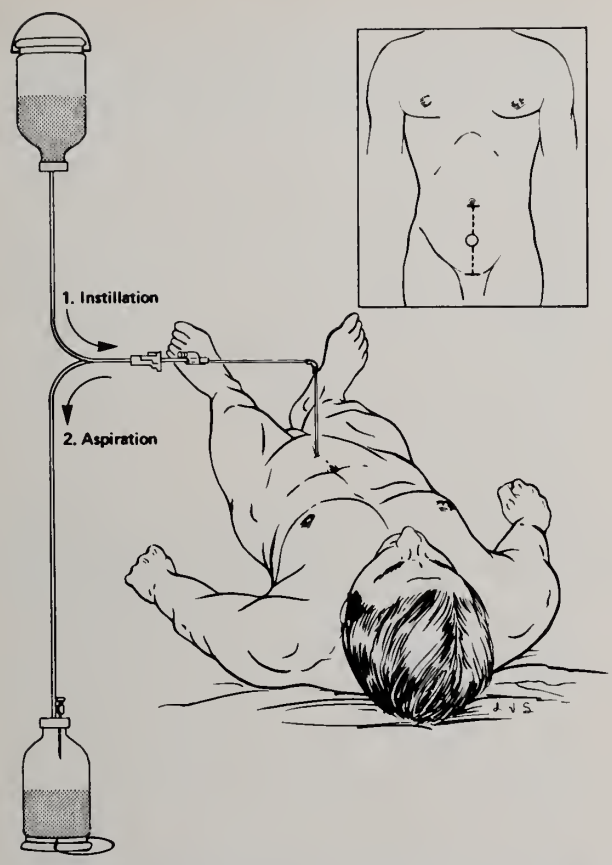


Figure 2.—Technique of peritoneal lavage. (From Dunphy JE, Way LW: Current Surgical Diagnosis and Treatment. Los Altos, CA, Lange Medical Publications, 1973.)

progressively deepens as it returns the test is unequivocally positive.

DR. BLAISDELL: *Doctor Lewis, you have surveyed the complications of peritoneal irrigation. Would you like to comment?*

FRANK LEWIS, MD:* I agree with Dr. Young's technique. One contraindication to peritoneal irrigation is the presence of scars on the abdomen from previous surgical operation. Adhesions increase the possibility of perforation of bowel, and previous operation generally contraindicates peritoneal catheterization. The risk of the procedure is related to the experience of the examiner. There is some possibility that the bowel, the mesentery or a retroperitoneal blood vessel will be perforated, although there have been no deaths or serious complications in several hundred peritoneal irrigations carried out at San Francisco General Hospital. The primary problem is the prospect of iatrogenic bleeding or injury to the bowel which demands laparotomy. The incidence of this complication is approximately 3 to 5 percent, but it is noteworthy that many of these patients would have required laparotomy because of the nature of their injury had peritoneal irrigation not been utilized.

*Attending Staff, San Francisco General Hospital.

DR. BLAISDELL: *Doctor Lewis, what is the incidence of false negative results of examination?*

DR. LEWIS: It is low, not more than 2 percent. We have assessed the significance of the color of the dialyzate by adding blood to a liter of saline solution. The addition of 5 ml of blood to a liter results in a salmon pink color, 10 ml a cherry red, and 15 ml an intense red. Therefore, the test is extremely sensitive for intraperitoneal bleeding.

DR. BLAISDELL: *I've said about all I need to say regarding the indication of a laparotomy. In this case the peritoneal irrigation was positive and this led to laparotomy shortly thereafter. I believe, however, that had we been content to observe this patient for another 4 or 5 hours, there would have been sufficient indication for laparotomy if a major injury was present. Could we hear what was found at operation?*

DR. YOUNG: At laparotomy there was approximately 300 ml of blood in the peritoneal cavity including several clots in the left upper quadrant. On careful examination the injury was found to be confined to a small tear of the spleen near the hilum which was oozing slowly during our period of observation. Splenectomy was carried out. The abdomen was closed in layers without drainage. The course thereafter was benign and the patient was discharged 5 days after operation.

A PHYSICIAN: *Doctor Blaisdell, this was a rather trivial hemorrhage. Do you think that the patient might have been all right had laparotomy not been carried out and splenectomy not done?*

DR. BLAISDELL: That is a very appropriate question, for the bleeding might have stopped and the volume might have been so small that laparotomy need not have been done. This case is a particularly appropriate one to discuss for that reason. When we are dealing with surgical problems relative to "the acute abdomen," most of our thinking is oriented to the possibility of appendicitis because of the potential lethal complications from unrecognized appendicitis which goes on to rupture and peritonitis. By the same token most of

our orientation relative to blunt abdominal trauma is directed toward the spleen. This is the one organ which is associated with a distinct possibility of late complications—the so-called "delayed rupture" of the spleen. I for one believe that there is no such thing as delayed rupture of the spleen. I have never known a case in which a patient who did not have frank hemorrhage at laparotomy, later had hemorrhage from delayed rupture of the spleen. The implication is simply this: The initial injury of the spleen produces a small hemorrhage which may not be recognized clinically. A hematoma accumulates in the splenic laceration. As this hematoma organizes it may expand secondarily as red cells contained within the hematoma break down, change osmotic forces and draw fluid into the lesion. This produces secondary expansion of the hematoma, which may further disrupt the splenic capsule, causing delayed hemorrhage. This possibility is most apt to occur within a day or two of the initial injury but we have seen delayed rupture occur as long as eight weeks afterward. For this reason, we feel there is no such thing as a benign splenic injury. The true incidence of delayed hemorrhage would be impossible to ascertain, for no one has the courage to observe the natural history of small traumatic rupture once the diagnosis has been made. I suspect that many patients with minor injuries of this type get along reasonably well. But if only 5 percent are at risk for a late hemorrhage, this is far too high. Trauma tends to occur in the young, active age group. The hemorrhage may occur at a time the patient is far removed from the hospital. Coroners' statistics attest that each year in San Francisco there are four or five deaths secondary to splenic rupture. Most of these are due to hemorrhage which occurs some time after the initial injury. Certainly we see one to two patients each year presenting in our Emergency Department with late hemorrhage from ruptured spleen. Doctor Muriel Steele has reviewed the complications of splenectomy. Doctor Steele, would you care to comment?

MURIEL STEELE:* We have recently reviewed 200 patients who underwent splenectomy for ruptured spleen at San Francisco General Hospital. In 64 the injury was limited to the spleen. In these patients, there were no significant complications—no subphrenic abscesses and no wound infections. There was one death due to pulmonary embolism seven days after splenectomy. In the remainder of the patients, who had splenectomy in association with multiple trauma, there was a 4 percent incidence of clinically significant pulmonary embolism. This incidence was of interest as we compared this group with a group of patients with comparable trauma who did not have splenectomy, most of whom had rupture of the liver. The incidence of pulmonary embolism in this latter group was approximately 0.25 percent.

A PHYSICIAN: *Do you place drains when splenectomy is done?*

DR. STEELE: As a matter of policy, no, except when there is associated injury such as pancreatic injury. In these circumstances, the secondary injury determines the indication for drainage. In the group of 200 patients we studied, only one had to be returned because of bleeding from the splenectomy bed.

We were surprised to find the high incidence of thromboembolic complications. These have been described as a complication of splenectomy and in the past it has been considered imperative to do serial platelet counts after the operation. If the count exceeded one million, anticoagulation was considered indicated. A certain negativism developed because it was found that there was no correlation between platelet counts and the risk of thromboembolic complications. I believe our indications for anticoagulation require reassessment on the basis of these statistics.

DR. BLAISDELL: I think we can conclude from this discussion that when we have blunt abdominal trauma, the orientation of the surgeon should be to the possibility of intraperitoneal bleeding. If there is blood loss going on somewhere and no obvious source, the probability is that there is intraperitoneal hemorrhage. An elevated leukocyte count with subtle abdominal changes on examination may be the only clue when the hemorrhage is minimal. If the injury involves the left upper quadrant, laparotomy is indicated, as rupture of the spleen is a likely possibility. Peritoneal lavage should be reserved for the patient with multiple injuries when abdominal assessment is difficult because of a depressed level of consciousness, thoracic injury or blood loss elsewhere.

*Assistant Chief, Surgical Service, San Francisco General Hospital; Associate Clinical Professor of Surgery, University of California, San Francisco, School of Medicine.

Refer to: Edwards WM Jr: Acupuncture in Nevada (Government and Medicine). West J Med 120:507-512, Jun 1974

Government and Medicine

Nevada's Senate Bill 448 was signed into law by Governor Mike O'Callaghan on 20 April 1973. The law permits the practice of Chinese medicine, including acupuncture, by practitioners who do not have to be physicians. The state legislature rapidly approved it with only two dissenters, one of them a physician.

Similar legislation may be considered in other states this year.

Acupuncture in Nevada

WILLIAM M. EDWARDS, JR., MD, MPH, *Carson City*

A LETTER recommending that a temporary special license be issued to Professor Lok Yee-Kung of Hong Kong for a demonstration of acupuncture was received 13 November 1972 by the Nevada State Board of Medical Examiners. Attached was a letter from Arthur Steinberg, president of the American Society of Acupuncture, Inc., of Las Vegas, describing the background and experience of Dr. Lok and a check for one hundred dollars to pay for the temporary licensure. The Board of Medical Examiners concluded that it was without authority, under existing laws and procedures, to issue a special license to practice acupuncture in the State of Nevada, and Professor Lok was so advised by letter and the hundred dollars was returned with the letter.

At its meeting 5 December 1972, the Board of Medical Examiners adopted the following position: "In the opinion of this Board of Medical Examiners, the practice of acupuncture constitutes the practice of medicine as defined by the statutes of the State of Nevada. Although acupuncture has been an important part of the theory and practice of Oriental medicine for several centuries, its concepts and uses are not understood by Western medicine; only recently has it been considered in the United States for its potential value. Very little scientific literature on this topic has been published in Western nations or even in China. Because of the lack of understanding by Western medical scientists, and because of potential harm which acupuncture might produce in patients for whom the treatment of symptoms would mask a serious or perhaps fatal condition otherwise amenable to treatment aimed at the cause, the Nevada State Board of Medical Examiners has concluded that at this time, acupuncture is not sufficiently well understood to be an acceptable method for use in the practice of medicine in this State."[1]

Nevada's legislature, which meets only every other year, started sessions beginning 3 January 1973, and the following resolution of the Nevada State Medical Association was forwarded to the Governor and to all legislators: "Be it resolved that the Nevada State Medical Association hereby petitions the Legislature to enact laws which will prohibit the use of acupuncture except by, or on the prescription of, a licensed doctor of medicine who is trained and equipped to diagnose and treat

The author is Chief, Preventive Medicine, Nevada State Health Division, and Secretary, Nevada State Board of Chinese Medicine.

Reprint requests to: W. M. Edwards, Jr., MD, MPH, Secretary, State Board of Chinese Medicine, 201 South Fall Street, Carson City, NV 89701.

disease, illnesses, injuries, and symptoms by means which are currently accepted by modern western medical science."[1]

On 7 March 1973, during a meeting of the Nevada State Board of Medical Examiners, Mr. Arthur Steinberg, a New York attorney and real estate developer who lives in semi-retirement in Las Vegas, hand-delivered a letter to the Board requesting, again, that a special license be issued to allow Professor Lok to demonstrate acupuncture before the Nevada State Legislature. Attached to the letter was a letter from Las Vegas Senator Lee Walker, chairman of the Senate Committee on Health, Welfare and State Institutions, inviting such a demonstration. The Board also received a telephone call from the May Advertising Agency, a public relations firm in Las Vegas, concerning the acupuncturist. The Board's representatives met with the Senate Committee on Health, Welfare and State Institutions on 8 March 1973.

On 12 March, S.B. 420 allowing demonstration of acupuncture was introduced in the state Senate as an "emergency bill" by the Committee on Health, Welfare and State Institutions in mimeograph form, and without printing, reading, or discussion, passed unanimously and was sent to the Assembly which passed it on March 13. The bill was enrolled and delivered to the Governor on March 14, and approved by him on March 15, effective the same date.[2] (Note, it is doubtful whether even a demonstration of acupuncture may be performed in most states without risk of the charge of "unauthorized practice of medicine.")

Letters and telephone calls from people all over the state and the nation who were interested in being treated by acupuncture began to deluge the Governor, doctors, and legislators. The May Advertising Company of Las Vegas helped spread the word.

On 14 March 1973, Senator Walker introduced S.B. 448,[3] authorizing the practice of Chinese medicine and acupuncture and providing for a State Board of Chinese Medicine as a regulatory body. The bill was quickly approved by both houses of the state legislature with only two dissenting votes, one of them by a physician, and was signed into law by Governor Mike O'Callaghan on 20 April 1973.

Dr. Lok demonstrated acupuncture from 19 March to 6 April 1973, in a clinic on the second floor of the Ormsby House, a hotel and casino across the street from the Nevada Legislative Building. Several hundred people were treated, including many legislators, and the great majority claimed improvement.

The Chinese Medicine Act

In S.B. 448,[3] "Acupuncture" means the insertion of needles into the human body by piercing the skin of the body, for the purposes of controlling and regulating the flow and balance of energy in the body. "Herbal medicine" and "practice of herbal medicine" mean suggesting, recommending, prescribing or directing the use of herbs for the cure, relief or palliation of any ailment or disease of the mind or body, or for the cure or relief of any wound, fracture, bodily injury or deformity. "Herbs" means plants or parts of plants valued for medicinal qualities. "Traditional Chinese medicine" means that system of the healing art which places the chief emphasis on the flow and balances of energy in the body mechanism as being the most important single factor in maintaining the well-being of the organism in health and disease and includes the practice of acupuncture and herbal medicine. "Licensed acupuncture assistant" means a person who assists in the practice of acupuncture under the direct supervision of a person licensed under the provisions of this chapter to practice traditional Chinese medicine or acupuncture.

The State Board of Chinese Medicine shall consist of five members appointed by the Governor. All must be citizens of the United States and residents of the State of Nevada. An Advisory Committee to the State Board of Chinese Medicine is created, and its members also appointed by the Governor. Members of the Advisory Committee "shall be selected with special reference to their ability and fitness to advise with respect to the duties of this chapter to the Board." Terms up to three years are specified for both the Board and for the Committee.

Section 14 states that the Board may waive examination and grant a certificate of Doctor of Traditional Chinese Medicine to any applicant who has applied in writing to the Board not later than 120 days after the effective date of the act, who has obtained a certificate from the Republic of China, the People's Republic of China, Korea or Japan acknowledging that the applicant was qualified to practice Chinese medicine, and who has practiced traditional Chinese medicine for at

least 20 years immediately prior to the effective date of this act.

The act became immediately effective upon passage and approval.

The Board of Chinese Medicine

During the last week of April and the first week of May, 1973, Governor O'Callaghan appointed the following five-man Board of Chinese Medicine: Neil Galatz, a Las Vegas attorney; William M. Edwards, MD, Chief of the Bureau of Community Health Services, of Nevada State Health Division in Carson City; Mrs. Barbara Greenspun, wife of the editor-publisher of the Las Vegas Sun newspaper, Robert McQueen, PH D, professor of psychology, University of Nevada, Reno; and John Holmes, MD, Las Vegas general practitioner.

The Advisory Committee to the Board of Chinese Medicine

From a host of names suggested by interested persons, volunteers, and satisfied patients, the Governor appointed the following knowledgeable persons to serve as the Advisory Committee to the Board of Chinese Medicine: Jane Lee, MD, 909 Hyde Street, San Francisco, California, general practitioner and graduate of the University of California School of Medicine; Madam Tom Po Chin, also of San Francisco; Chester Chin, DC, currently president of Nevada Chiropractic Association, a graduate of the National Taiwan University Medical School, who has offices in Las Vegas; Yiu-Wing Choi, MD, graduate of Peking Medical School, currently working in the temporomandibular joint pain clinic of the University of Southern California School of Dentistry; and Professor Lok Yee-Kung, who had returned to his practice of Chinese medicine in Hong Kong following his demonstration before the Nevada State Legislature.

The First Meeting of the Board of Chinese Medicine

The Board, at its first meeting, 15 May 1973, agreed that it would not waive the examination for anyone despite its lawful authority to do so in Section 14. Following the advice of its Advisory Committee, the Board voted unanimously to require that all applicants pass an examination given by the Board before issuance of a license.

One major problem facing the Board was money. No funding was provided in S.B. 448 as it passed through the Legislature. The law merely provided that a person applying for a license must pay a $100 fee and every person holding a license who is a resident of the state should pay an annual registration fee of $20. Non-residents who are licensed must pay an annual registration fee of $5.

On 5 July 1973, the Board of Chinese Medicine approached the Nevada Interim Finance Committee of the State Legislature, which voted to loan the Board of Chinese Medicine $8,300 start-up money.

The Application Form

The eight-page license application form, its three-page instruction sheet, and a copy of the law were mailed to some 160 potential applicants on 16 August 1973. More than 40 went to the Orient, about 60 to addresses in California, and the rest to residents of other states and countries.

The application provides a space for the applicant to indicate whether he wishes to apply for licensure in (1) Traditional Chinese Medicine, (2) Herbal Medicine, (3) Acupuncture, or (4) Acupuncture Assistant. Space is provided for the applicant to list his schools or training, preceptors, location, years attended, degree if any, and year of degree.

One section of the Application Form reads as follows: "A non-refundable fee of $100 must accompany the application. Diplomas, transcripts, other licenses, and a Certificate of Competency from the Government of the Republic of China, Peoples' Republic of China, Korea or Japan must be sent directly to the Secretary, Board of Chinese Medicine for the issuing agency whenever possible. Clearly readable photostatic copies are acceptable. No certificate as to the possession of these credentials will be accepted in lieu thereof. All applications must be on file with the Secretary of the Board of Chinese Medicine at least three months prior to the date of examination."

History of years of practice is required, with inclusive dates. Also required are date and place of birth, places of residence for the past 10 years, citizenship and immigration data, social security number, military service, membership in societies, arrest records, affidavits of professional and moral character, photograph, fingerprint cards, name written in Chinese, identification numbers in foreign countries, if any, and other appropriate information.

A "Consent to Investigation" is also part of the application, and must be signed by the applicant.

It states: "I do hereby give my consent to any investigation by the Nevada Board of Chinese Medicine, or any person acting in its behalf, into all relevant facts in my personal and professional training, background and experience in connection with this application for a license to practice Traditional Chinese Medicine, Herbal Medicine, Acupuncture or Acupuncture Assistant (circle one) in the State of Nevada. I do further consent to having a set of my fingerprints submitted to any law enforcement agency in connection with this application. I do further agree to pay any and all costs or expenses incurred in the making of the required investigation and do herewith submit as part of this Application a deposit of $300 to be used in whole or in part for said investigation."

Also included in the application is the following paragraph:

"An applicant, if issued a license, agrees to permit the Board of Chinese Medicine, or its designee, to observe and monitor any and all aspects of the licensee's practice, including clinical techniques, record keeping, treatment outcomes, ethics and professional conduct, referral practices, fees charged, treatments given at no charge, collection methods, research, and similar or related data."

Another section of the application states: "Before a licensee can practice Chinese medicine, evidence of satisfactory professional liability insurance must be on file with the Secretary, Board of Chinese Medicine." (Author's note: Apparently no such insurance for non-physicians is available at this time, according to information available.)

The Board's standard investigation at this time includes: fingerprint check through Federal Bureau of Investigation, overseas investigators, U.S. Immigration Service, U.S. Internal Revenue Service, consumer fraud departments of cities, counties, and states, appropriate state medical associations, foreign medical associations, and appropriate state boards of medical examiners.

Provisional licensing is not possible under S.B. 448.

Preparation of the Test

The Board of Chinese Medicine's Advisory Committee bears the main responsibility for testing the applicants, and its Advisory Committee prepares all the test questions. The Advisory Committee members also conduct the oral and practical demonstration portions of the test and grades the test.

Dr. Thomas Cassese, professor of education, University of Nevada, Las Vegas was placed under contract to the Board to provide consultation services for the preparation, administration and grading of examinations.

The format for the first test to be given at the University of Nevada, Las Vegas, December 6, 7, and 8, 1973 was as follows: The first day of the examination was written, and covered questions pertaining to basic medical sciences in the morning and herbology in the afternoon. The second day was also written and covered part B of herbology for those wishing licenses only in Herbal Medicine, or covered acupuncture and traditional Chinese medicine questions for the other applicants. The third day, December 8, covered English speaking ability and aspects of Chinese medicine and was both oral and practical.

Applicants were given a choice of whether they wished to take the written portions of the examination with the questions prepared in English or in Chinese or both. All except the one white candidate requested both versions.

Licensing of the Advisory Committee

The Board of Chinese Medicine at its meeting in Las Legas on 13 November 1973, reviewed the investigators' reports on the individual members of the Advisory Committee. Licenses were issued to Chester Chin, DC, licensed to practice Traditional Chinese Medicine; Dr. Tom Po Chin, licensed to practice Traditional Chinese Medicine and Acupuncture; Professor Lok Yee-Kung, to practice Traditional Chinese Medicine; and Jane Lee, MD, to practice Acupuncture. Dr. Jane Lee had been examined by the Nevada State Board of Medical Examiners and licensed to practice medicine in Nevada on 5 September 1973. The investigators' report on Yiu Wing Choi, MD, was not complete at that time, but the Board voted to license Dr. Choi at the time of his complete clearance by its investigators. He was licensed 31 January 1974, to practice Traditional Chinese Medicine.

The Candidates

At the time of the first test, December 6, 7, and 8, 1973, 34 candidates had completed their applications to the Board of Chinese Medicine.

Twenty of the candidates indicated residence in

California; three in Hong Kong; two in New York; one in Canada; two from Taiwan; two from Korea; and one each in Maryland, Virginia, Washington D.C., and Florida. Candidates were all of oriental extraction, with the exception of one white woman. Eight had Korean names, and the rest had Chinese names. There were no Japanese candidates. There were no candidates from the People's Republic of China. Only one candidate indicated that he wished to be licensed only in Herbal Medicine. At least 11 indicated they had MD degrees in their own countries. One was a dentist. Two are licensed to practice medicine in the United States, one of them in South Dakota and the other in New York. Many indicated that they came from families of several generations of acupuncturists.

The Practice of Chinese Medicine and Acupuncture by Licensed Physicians

Under the opinion of the Nevada State Attorney-General's office, dated 27 August 1973, the current position of the Nevada State Board of Chinese Medicine is that medical doctors and osteopathic physicians properly trained in acupuncture may add acupuncture as a method of treatment in their medical practice without additional licensing from the Board of Chinese Medicine. However, under the Chinese Medicine Act, any doctor who holds himself out to the public as an acupuncture specialist is required to first obtain a license as a doctor of acupuncture from the State Board of Chinese Medicine and meet all the pertinent requirements of law and regulation.

Public Wants

There were tremendous surges of public pressure to speed up the licensure of acupuncturists in Nevada during the period covered by this report. Conversely, there was almost no demand to speed the licensing of practitioners of herbal medicine. The Board of Chinese Medicine received hundreds of letters of inquiry and phone calls from all over the nation from people wishing to have acupuncture treatment in Nevada. The Board was accused of "dragging its feet" in implementing licensing of procedures and of being "a do-nothing" board. The man in the street seemed to be convinced that the Board took more than a year to license even the first members of the Advisory Committee.

Board meetings must be open to the public by law in Nevada. Typical comments from the audience in November, 1973 meetings included: "Sooner or later, why not now?"; "The Legislature wanted it done immediately"; "The Board should be replaced"; "You are working for the AMA"; "Why aren't you licensing those who are qualified?"; "You are making the Governor look bad"; "The Board should be more sensitive"; "You don't need to investigate Dr. Lok"; "If the FBI has cleared an acupuncturist, that should be sufficient"; "License now"; "Procrastination"; "License first, then withdraw the license if the acupuncturist gets into trouble"; "Dr. Lok proved himself in Carson City"; "We demand immediate licensure today of Dr. Lok"; "The Board is preventing qualified acupuncturists from treating people who need treatment now"; "License acupuncturists regardless of investigation"; "You keep throwing obstacles in the way"; and others. There was a strong faction who wished to have Professor Lok Yee-Kung licensed immediately.

The Board, on the other hand, and backed by its Advisory Committee, felt that no licenses should be issued to anyone until his background and credentials had been thoroughly checked by its investigators.

Relationships with Physicians

Relationships with the Nevada State Medical Association by the Board of Chinese Medicine have always been good during this rather trying period. Collection and evaluation of acupuncture treatment data have been assumed by the Nevada State Medical Association. The Association approved a resolution during its recent annual meeting in Las Vegas for the establishment of an "Acupuncture Results Depository" which will accept from physicians any substantive reports, good or bad, regarding acupuncture treatment as related to them by patients or observed by them in subsequent care of such patients.

Association President Dr. Thomas K. Hook of Elko has said: "During the furor over passage of the acupuncture licensure law in the last session of our legislature, it somehow came out that physicians were against acupuncture per se. Actually we are pretty much together on the idea that it should be studied before it is approved for general application, the same as any other form of therapy."

It is of interest to note that physicians may refer patients to practitioners of Chinese medicine. The Judicial Council of the AMA has given the

opinion that a referral to a paramedical consultant is completely ethical if referral is not for medical opinion.

The Tests

The first test, given in Las Vegas, December 6, 7, 8, 1973, was graded and the test scores made final by the testing consultant. The final background checks are being completed, and the licensing of twelve candidates who successfully passed the examination was performed 13 March 1974, by the Board of Chinese Medicine. As of 15 March 1974, there were 17 acupuncturists licensed in Nevada.

Nevada Board of Chinese Medicine

At its meeting in Las Vegas 13 March 1974, the Nevada Board of Chinese Medicine licensed 11 more practitioners of Chinese medicine. These are in addition to the five members of the Advisory Committee who were licensed in November, 1973, and in January, 1974. One additional practitioner will be licensed as soon as clearance is received from the Board's investigators in the Orient.

Three were licensed as Doctors of Acupuncture and one was licensed as a Doctor of Traditional Chinese Medicine. The four applicants, who are classed as "master acupuncturists," scored in at least the 75th percentile in the December 6, 7, and 8, 1973, exams administered at the University of Nevada, Las Vegas. Twenty-four candidates took the examination.

The eight applicants scoring between the 50th and 75th percentiles were licensed as Acupuncture Assistants even though three had applied for licensing in Traditional Chinese Medicine and two as Doctors of Acupuncture.

Comment

Responsible practitioners of the Chinese healing arts are quick to caution that there are many conditions which will not respond to acupuncture any better than they have to Western medicine. In some diseases and conditions, acupuncture may well be the preferred form of treatment.

The five members of Nevada's state licensing board have been moving through the licensing process very carefully, despite a great deal of public pressure for quick action. Other states may be pressed in a similar fashion and physicians are reminded to take thought from the Nevada experience.

Although the Nevada statute exempts licensees from liability for the unlicensed practice of medicine, licensed applicants must fulfill stringent requirements. These provisions, including a ten year experience requirement, indicate that the statute is somewhat less than an open invitation to practitioners of the Chinese healing arts in Nevada. Readers are referred to Laws of Nevada, 1973, Ch. 441, p. 635, et seq.

The Nevada Board of Chinese Medicine will continue to follow acupuncture and report on it regularly.

REFERENCES

1. Nevada State Medical Association News, Vol. 20: Apr 1973
2. Senate Bill 420, Introduced into Nevada State Legislature by Senate Committee on Health, Welfare, and State Institutions, Mar 12, 1973
3. Senate Bill 448, Introduced into Nevada State Legislature by Senator Lee Walker, Mar 13, 1973

Refer to: Rapaport SI: Research in medical schools—A personal view (Informed Opinion). West J Med 120:513-515, Jun 1974

Informed
OPINION

Research in Medical Schools
—A Personal View

SAMUEL I. RAPAPORT, MD, *Los Angeles*

WHEN THE ATTACKS upon research activity in medical schools began, I was puzzled and angered by them. I had no quarrel in principle with the words of an editorial in the *New York Times* which stated, "Academic specialists, in common with any special interest group, deserve to pass through periodic review of their value to society at large." But I know that I agreed so readily with these words because I was convinced that we would come through such a review with flying colors. Would anyone have serious trouble in seeing that the investment in biomedical research of the past 25 years had paid off not only in an explosion of biomedical knowledge but in revolutionary advances in patient care? And wasn't just about everyone in on the secret that the money had also been spent-twisted-and-stretched to pay for a variety of programs which had also improved the quality of clinical teaching?

Nevertheless, I had trouble in suppressing an uneasy feeling that a segment of the academic community had exhibited signs of an exaggerated commitment to research. Some of our brightest young graduates seemed infected with a virus, a virus containing an enzyme which one friend of mine has called Atlantic City transcriptase. Those infected understood instinctively that a bibliography of substance was the *sine qua non* for admission to our academic societies and for tenure in our medical schools, and they wasted no time in minimizing activities interfering with its rapid acquisition. I felt sorry for colleagues so heavily infected that they seemed to have lost all regard for clinical activities. I thought that they were missing out on a feeling important for all doctors and teachers of doctors—that special quality of satisfaction that stems from seeing very sick patients through complicated illness. And a number developed a serious late complication of the virus; as their clinical skills dried up, so did their research productivity. They found themselves masters of research skills which had outlived their usefulness in today's fast-changing biomedical research scene.

Nonetheless, the majority of those I knew in academic medicine seemed to have struck a reasonable balance, in which they maintained clinical responsibilities and activities. Certainly, our medical schools were prospering. Laboratories, departments and faculties grew as the soft money rolled in through the 1950's and on into the late 1960's. Subspecialties prolifererated, almost malignantly, to accommodate our new biomedical knowledge, as did new societies, meetings and journals. The biomedical research dollar was there; it was in the national interest to spend it—and times were good.

I am not sure who it was who first looked out the window and told us that we were missing 60,000 physicians out there. To this day I don't know how that particular number was generated, but few would deny that a real and serious shortage was suddenly apparent. It had features similar to today's energy shortage. Few had appreciated the size of the shortfall that was coming. We had no advance plans to counter it, and we had masked its early stages by steadily increasing foreign imports.

Searching for fast answers for our predicament,

The author is Professor, Department of Medicine, and Head, Hematology Division, University of Southern California School of Medicine, Los Angeles.

Presidential Address, Western Association of Physicians Nineteenth Annual Meeting, February 6, 1974, Carmel, California.

Reprint requests to: S. I. Rapaport, MD, Department of Medicine, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles, CA 90033.

some were quick to point a finger of blame at biomedical research activities. Clearly, however, the shortage couldn't be accounted for by a simple process of subtraction. Thousands of young doctors had not been drawn away from the bedside into laboratories to mind rats, rabbits and chromatographic columns. A withdrawal of effort from patient care into laboratory research was not an important cause for the shortage. But flow in the opposite direction was. The new biomedical knowledge arising from laboratory research had not been left to lie unlinked to patient care, as some of our recent medical students, obsessed with immediate relevance, seemed to believe. Within a short time an enormous mass of knowledge from the laboratory had been applied to clinical activities, but with little logistical planning for the demands upon our medical resources which non-Gompertzian growth of complex diagnostic and therapeutic modalities would create. We kept producing doctors at the same rate while we multiplied the things that they were able to do —and that they wanted to do because they were exciting and worth doing. Depending upon your orientation, you could blame or thank biomedical research for that.

In trying to close the gap, those controlling the manna from Washington decided to slow down the science, to dim the lights. They slashed biomedical research funds, without appreciating the scope of activities those funds supported. We were trapped in the predicament that accountants in Washington had believed us when we said that we were spending all that money solely on research, and we couldn't now convince them that we had all been gentlemen liars in a good cause. At the moment when we most needed training grants, fellowships and other grant funds to expand faculties to keep pace with expanding student bodies and newly-opening medical schools, these funds began to disappear.

What complicated things further was the emergence of a significant block of physicians and educators who believe that a faculty oriented towards research as well as teaching represents an unnecessary luxury in medical education. At least two medical schools, whose students may spend the major portion of their time away from the university in community hospitals, are testing the hypothesis that functions and activities beyond instruction are unnecessary to provide an environment for producing a qualified physician. In all fairness, I must admit that it is too early to judge the result, and indeed I suspect that it may prove impossible to evaluate this experiment objectively. In the meantime, in the words of the late Samuel Goldwyn, "Include me out." I fear that students in such schools are short-changed. I hold firmly to the prejudice that a solid exposure of students to a clinical faculty involved in research provides a qualitatively different experience of importance, if for no other reason than that it exposes students *at the bedside* to questioning, restless minds dissatisfied with current explanations. How else can medical students develop the insight needed to examine critically their own activities, which is their major weapon against the built-in obsolescence of everyone's medical education?

However, a serious challenge to the legitimacy of research activity in medical schools has arisen. It stems from the increasing emphasis of the National Institutes of Health upon the support of mission-oriented research built around contracts and large categorical centers. Louis Pasteur's epigram, "Chance favors the prepared mind," served us well as a touchstone for national biomedical research policy. Funding based upon this principle led to the opening up, one after another, of new fields of research activity; to the training of a generation of biomedical investigators in the United States second to none; and, most significantly for the university community, to the creation of the scholarly and critical environment in our schools of medicine so important, as I have already stressed, for the education of thinking physicians with staying power.

What a calamity to have this free approach encroached upon by a restrictive system of contracts in which medical faculty hire out to do jobs someone else had decided needs doing—and under rules severely limiting independent, innovative activity. Such contracts are for private companies in the research business. No matter how tempting the money or how dire the need, members of the university community should respond as a faculty and say, "Our services are not for sale on this basis." Indeed, I believe that an individual faculty member who wishes to negotiate a contract should first have to establish, before a committee representative of the faculty at large, that his proposal has academic merit within the goals and priorities of that faculty. If we do not limit our participation in contract research by some such mechanism, I have a feeling that we are buying a ticket on the Titanic.

I am less sure of what to think about the de-

velopment of large NIH-supported categorical "centers" within schools of medicine. Such centers offer a unique opportunity to bring together a critical mass of investigators in a concentration area. They also provide an administrative mechanism for basic scientists and clinical investigators to work together freed from the constraints frequently imposed by the traditional departmental structure of medical schools. Obviously, these are good things. Yet, I resent the availability of many millions of dollars for centers, when it is coupled with the unavailability of a few dollars to help a promising young investigator who wants to go his own way. And I worry that a lot of mediocrity can hide within a center. I also am concerned about the effect upon the university environment of double systems of allegiance. What will it mean to accumulate large numbers of faculty who split their allegiance between the school of medicine as a whole and a center as a separate entity within the school? And how will a center balance its responsibilities for university functions with its responsibilities for NIH-directed functions? Clearly, much will depend upon the goals and human qualities of the people who set policy within each institution. And much will also depend upon the strength of the university. A medical school must be strong to support a center. Adding a center to a school of medicine with weak foundations will cause the whole institution to tilt.

Finally, I want to express my opinion that clinical research activity cannot function as something separate within a medical school. It must blend with everything else that is going on. Clinical research acquires full legitimacy within the medical school environment only when the clinical teaching and patient care activities of the medical school function well. As we all know, it takes many kinds of people, with diverse talents, to make this happen. Unfortunately, university promotion policies and membership requirements of our research societies sometimes act as divisive forces to make research seem a more worthwhile medical school function than teaching and patient care. The faculty member with a strong research commitment and the faculty member involved primarily in teaching and clinical care share responsibility, as equals, for the overall prospering of the medical school. Excellence in all areas is required to preserve and enlarge the academic environment. If only for our own enlightened self-interest, those of us involved in research activities should support, wholeheartedly, the fight for equal academic recognition of our colleagues engaged primarily in teaching and patient care.

I realize that my remarks here represent only my rough approximations of the way things really are. In presenting such rough approximations, I take comfort from the thought that it is better to be roughly right than precisely wrong.

82nd ANNUAL MEETING
IDAHO MEDICAL ASSOCIATION

Sun Valley, Idaho
July 24-27, 1974

Guest Speakers

LENDON H. SMITH, MD, Portland, Oregon

All About the Hyperactive Child

How to Win at the Office Without Cheating

Sex Education and the Adolescent Child

RONALD J. PION, MD, Honolulu, Hawaii
Director, Family Planning Program, Kapiolani Hospital
Professor, Department of Obstetrics and Gynecology
University of Hawaii School of Medicine

The Office Management of Sexual Problems

The Role of the Hospital in Preventing Unplanned Conception

EUGENE J. VAN SCOTT, MD, Philadelphia, Pennsylvania
Professor of Dermatology, Temple University School of Medicine

Common Adolescent Skin Disorders—Warts, Rashes, Zits

Psoriasis—Its Topical and Systemic Management

Drug Combinations in Dermatologic Therapy

JOHN L. BOYER, MD, San Diego, California
Associate Professor, San Diego State University
President's Council on Physical Fitness and Sports

Current Status of Coronary Artery Disease

The Physical Conditioning of Physicians

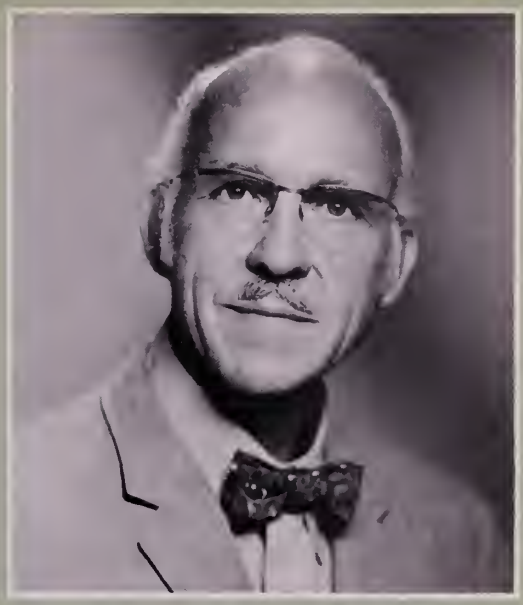
LEWIS A. KIRSHNER, MD, Cambridge, Massachusetts
Clinical Associate in Psychiatry, Mount Auburn Hospital
and Research Associate, Harvard Health Services

Mixed-Up Crazy Kids

Psychologic Aspects of Abortion

An Invitation to
SUN VALLEY

July 24 - 27, 1974



E. R. W. FOX, MD, *President*
Idaho Medical Association

It is my pleasure to extend a most cordial invitation to physicians in the west to attend the 82nd annual meeting of the Idaho Medical Association at beautiful Sun Valley, July 24-27, 1974.

We feel that our annual session is unique among medical meetings. There is a substantial scientific program arranged with the interests of generalists and specialists in mind.

A delightful social program is planned, and there will be ample time for enjoying almost every imaginable summer recreational activity—golf, swimming, tennis, riding, sightseeing and countless more, including ice-skating.

The result is a meeting which offers an opportunity for a memorable summer break for the entire family.

We hope that you will be with us at Sun Valley.

Sincerely,

E. R. W. FOX, MD, *President*
Idaho Medical Association

For registration and reservation information:

ARMAND L. BIRD, *Executive Director*
Idaho Medical Association
407 West Bannock
Boise, Idaho 83702
(208) 344-7888

in memoriam

ALLEN, JAMES STRATFORD, Woodland Hills. Died February 28, 1974 of cancer, aged 76. Graduate of the College of Osteopathic Physicans and Surgeons, Los Angeles, 1927. Licensed in Calfornia in 1928. M.D. degree from California College of Medicine, 1962. Doctor Allen was a retired member of the Forty-First Medical Society and the California Medical Association, and an associate member of the American Medical Association.

ALLISON, HARRY B., Apple Valley. Died April 16, 1974 in Apple Valley of cancer of the lung, aged 71. Graduate of the University of Oregon Medical School, Portland, 1929. Licensed in California in 1929. Doctor Allison was a retired member of the San Bernardino County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

ATHANASIOU, ATHANASIOS, San Francisco. Died March 13, 1974 in San Francisco, aged 71. Graduate of National University of Athens School of Medicine, 1926. Licensed in California in 1953. Doctor Athanasiou was a member of the San Francisco Medical Society.

BEGGS, JAMES HENRY, Upland. Died December 12, 1973 in San Bernardino of heart disease and bronchopneumonia, aged 82. Graduate of the College of Physicians and Surgeons, Los Angeles, 1917. Licensed in California in 1917. Doctor Beggs was a retired member of the San Bernardino County Medical Society and the California Medical Association, and an associate member of the American Medical Association.

BENNETT, EVERETT E., Lodi. Died March 21, 1974 in Lodi, aged 73. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1934. Licensed in California in 1934. Doctor Bennett was a member of the San Joaquin County Medical Society.

BERLIN, ANTHONY S., Anaheim, Died December 7, 1973 of disseminated malignant lymphoma, aged 66. Graduate of the University of Minnesota Medical School, Minneapolis, 1937. Licensed in California in 1947. Doctor Berlin was a member of the Orange County Medical Association.

BRIDGMAN, OLGA, Hillsborough. Died February 6, 1974, aged 87. Graduate of the University of Michigan Medical School, Ann Arbor, 1910. Licensed in California in 1917. Doctor Bridgman was a member of the San Francisco Medical Society.

BURCH, JOHN THOMAS, San Pedro. Died March 24, 1974 in Long Beach of injuries received in an automobile accident, aged 49. Graduate of University of Southern California School of Medicine, Los Angeles, 1952. Licensed in California in 1952. Doctor Burch was a member of the Los Angeles County Medical Association.

BUTLER, GEORGE A., Eldridge. Died February 21, 1974 in Santa Rosa of arteriosclerotic heart disease, aged 62. Graduate of the University of California Medical School, Berkeley-San Francisco, 1947. Licensed in California in 1948. Doctor Butler was an associate member of the Sonoma County Medical Association.

CABRERA, EUSEBIO EMMANUEL, Torrance. Died March 30, 1974 in Riverside of injuries received in plane crash, aged 38. Graduate of Wayne State University College of Medicine, Detroit, 1963. Licensed in California in 1964. Doctor Cabrera was a member of the Los Angeles County Medical Association.

CROCKETT, HERBERT GILLIS, Los Angeles. Died February 22, 1974 in Los Angeles of heart disease, aged 66. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1934. Licensed in California in 1935. Doctor Crockett was a member of the Los Angeles County Medical Association.

DEEB, PAUL H., Corona. Died March 2, 1974 in Corona, aged 56. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1942. Licensed in California in 1942. Doctor Deeb was a member of the San Bernardino County Medical Society.

GREENBERG, ALFRED, Tarzana. Died April 14, 1974 in Tarzana of heart disease, aged 49. Graduate of the Chicago Medical School, 1951. Licensed in California in 1953. Doctor Greenberg was an associate member of the Los Angeles County Medical Association.

GRIECO, SEBASTIAN C., Berkeley. Died March 24, 1974 in Berkeley of heart disease, aed 64. Graduate of St. Louis University School of Medicine, 1941. Licensed in California in 1943. Doctor Grieco was a member of the Alameda-Contra Costa Medical Association.

HALE, DONALD E., San Diego. Died November 9, 1973 of heart disease, aged 70. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1929. Licensed in California in 1968. Doctor Hale was a member of the San Diego County Medical Society.

HARRISON, CHARLES WILLIAM, JR., Redlands. Died March 24, 1974 in Desert Hot Springs, aged 54. Graduate of the University of Sydney Medical School, Sydney, 1943. Licensed in California in 1949. Doctor Harrison was a member of the San Bernardino County Medical Society.

IRWIN, RALPH L., Los Angeles. Died April 4, 1974 in Santa Monica of complications of surgery, aged 74. Graduate of the State University of Iowa College of Medicine, Iowa City, 1925. Licensed in California in 1941. Doctor Irwin was a member of the Los Angeles County Medical Association.

KAVINOKY, NADINA R., Newport Beach. Died November 24, 1973 in Newport Beach of cancer, aged 85. Graduate of State University of New York at Buffalo, School of Medicine, 1910. Licensed in California in 1921. Doctor Kavinoky was a retired member of the Orange County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

LASIN, HARRY, Culver City. Died March 28, 1974 in San Luis Obispo, aged 61. Graduate of the University of Illinois College of Medicine, Chicago, 1937. Licensed in California in 1937. Doctor Lasin was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

LOSEOFF, THEODORE ALLAN, Los Angeles. Died February 23, 1974 of heart disease, aged 42. Graduate of the Chicago Medical School, 1960. Licensed in California in 1961. Doctor Loseoff was a member of the Los Angeles County Medical Association.

MAND, LOUISE AUERBACH, Los Angeles. Died April 21, 1974 in Los Angeles, aged 89. Graduate of Cornell University Medical College, New York, 1911. Licensed in California in 1913. Doctor Mand was a retired member of the Los Angeles County Medical Association and the California Medical Association, and an associate member of the American Medical Association.

NESSELROD, JERROLD P., JR., Orange. Died April 10, 1974 in Garden Grove, aged 41. Graduate of Northwestern Medical School, Chicago, 1958. Licensed in California in 1960. Doctor Nesselrod was a member of the Orange County Medical Association.

PAYNE, ROSS A., Santa Ana. Died March 5, 1974, aged 61. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1951. Licensed in California in 1951. M.D. degree from California College of Medicine, 1962. Doctor Payne was a member of the Orange County Medical Association.

ROACH, FRANCIS XAVIER, JR., Stockton, aged 54. Was shot by an assailant on March 11, 1974 in Stockton. Graduate of the University of Minnesota Medical School, Minneapolis, 1942. Licensed in California in 1946. Doctor Roach was a member of the San Joaquin County Medical Society.

SCHMITT, GEORGE DONALD, Panorama City. Died April 11, 1974 in Northridge of heart disease, aged 51. Graduate of Marquette School of Medicine, Milwaukee, 1946. Licensed in California in 1952. Doctor Schmitt was a member of the Los Angeles County Medical Association.

SICHERMAN, KARL L., Tarzana. Died February 22, 1974 in Tarzana of renal failure and heart disease, aged 67. Graduate of the University of Michigan Medical School, Ann Arbor, 1931. Licensed in California in 1932. Doctor Sicherman was a member of the Los Angeles County Medical Association.

STEPHENS, LORIN L., Arcadia. Died March 24, 1974 in Arcadia, aged 48. Graduate of Temple University School of Medicine, Philadelphia, 1948. Licensed in California in 1949. Doctor Stephens was a member of the Los Angeles County Medical Association.

SWEEDLER, DANIEL ROBERT, Livermore. Died March 17, 1974 in Livermore, aged 40. Graduate of Yale University School of Medicine, New Haven, 1958. Licensed in California in 1964. Doctor Sweedler was a member of the Alameda-Contra Costa Medical Association.

TALBOT, HARRY F., JR., San Diego. Died March 16, 1974 in San Diego of heart disease, aged 60. Graduate of Des Moines Still College of Osteopathy, Des Moines, 1950. Licensed in California in 1951. M.D. degree from California College of Medicine, 1962. Doctor Talbot was a member of the San Diego County Medical Society.

WOOD, LAURIN L., Los Angeles. Died March 31, 1974 in Los Angeles of heart disease, aged 77. Graduate of Northwestern University Medical School, Chicago, 1926. Licensed in California in 1927. Doctor Wood was a member of the Los Angeles County Medical Association.

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

EMBRYOLOGY FOR SURGEONS—The Embryological Basis for the Treatment of Congenital Defects—Stephen Wood Gray, PhD, Professor of Anatomy, Emory University School of Medicine, Scientific Staff, Emory University Hospital, Consultant to the Piedmont Hospital Medical Staff for Congenital Anomalies, Atlanta; John Elias Skandalakis, MD, PhD, Professor of Anatomy, Emory University School of Medicine, Senior Attending Surgeon and Director of Medical and Surgical Education, The Piedmont Hospital, Adjunct Professor of Management and Health Administration, Georgia State University, Atlanta. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1972. 918 pages, $36.

This superb book contains 28 chapters which are divided anatomically. There are 8 chapters which cover the gastrointestinal tract from the pharynx and its derivatives (branchial apparatus, thyroid, parathyroid, and thymus glands) to the colon and anus. Four chapters discuss the respiratory system, pulmonary circulation and diaphragm. There is one section on the body wall, including omphalocele, gastroschisis, etc. Seven chapters encompass the genitourinary tract, adrenal glands, gonads and sex determination. Six chapters describe the circulatory system, including the lymphatics, heart, and great vessels. The final chapter treats asymmetry and splenic anomalies. Each chapter provides a general description of the regional anatomy, embryogenesis of the part, history, incidence of malformation, clinically important anomalies, and the symptoms, etiology and treatment of the anomalies. Extensive historical references are at the end of each chapter. Pictures and drawings are taken freely from original articles, and they are supplemented very nicely with original diagrams. The text is well written, and in many instances it is masterful in avoiding favored theories or emphasis on controversial issues.

Some differences or omissions from current concepts in pathogenesis and treatment may be found. Examples include: (1) origin of medullary carcinoma of the thyroid from the ultimo-branchial bodies is not described, (2) a need to stress the superior efficacy of techniques such as resection and end-to-oblique anastomosis for small bowel atresia, (3) the authors have wrongly deemphasized the significance of pulmonary hypoplasia associated with congenital diaphragmatic hernia, (4) gastroschisis is described as " . . . herniation . . . through a congenital muscular defect in the abdominal wall . . ." although pediatric surgeons find that it is a midline defect adjacent to a normal umbilical cord with or without a bridge of skin between the cord and the defect, (5) more recent methods of treatment and survival results for omphalocele and gastroschisis should be cited.

Because the book was printed in 1972, there are few references after 1964, when many newer concepts in embryogenesis and treatment have been developed. However, the extensive list of references cited is very valuable for historic tabulation.

Some prior knowledge of embryology is probably necessary, but this book provides an excellent and concise recall of embryology. This book would be an excellent reference for students in embryology who would gain from the clinical perspectives included. It is a valuable book for pediatricians, general surgeons, urologists and cardiac surgeons in enhancing background knowledge in a rapid and informative way.

ALFRED A. DELORIMIER, MD

* * *

INFECTIOUS DISEASES—Edited by Paul D. Hoeprich, MD, Professor of Medicine and Pathology, and Chief, Section of Infectious and Immunologic Diseases, School of Medicine, University of California, Davis, California. Harper & Row, Publishers, Medical Department, 2350 Virginia Avenue, Hagerstown, Md. (21740), 1972. 1,300 pages, 180 illustrations, $42.50.

Dr. Hoeprich is well recognized as an international authority on infectious diseases and has compiled a timely and significantly different textbook on this field. The book is heavy, six pounds, six ounces, the print is large and empty pages separate the chapters. This makes for easy reading, especially for those afflicted with presbyopia but difficult portage and expensive binding. It is not a handbook. There are 89 eminent contributors and 154 chapters including a fascinating section on presumed or possibly infectious diseases. Although there is a section on control of infectious disease, hospital epidemiology is not incuded. His comprehensive coverage of his field allows only limited space for each subject. This has been done very well with the authors adhering to a common organization of material within each chapter. It is in the overall organization of subject matter that his book differs importantly from other infectious disease texts. His major sections are by organ system. There are difficulties with any system of classification and there are certainly problems with this one, but the benefits for the medical students and the practicing physician are great. The organ system approach is very clinical and allows for good discussion of areas usually poorly covered. For example, recurrent urinary tract infections, pancreatitis, subphrenic and other intra-abdominal abscesses to name a few. The general strengths as well as weaknesses of his approach are succinctly described in his own preface which is only two pages long, and I recommend their perusal to individuals considering purchase. I definitely recommend this volume to hospital libraries.

In summary, Dr. Hoeprich compiled a most useful book of infectious diseases. The subject matter is deliberately too condensed to be of great help to consultants in infectious disease and the organ system approach to organization of material may not appeal to microbiologists who will now have to look in the index instead of the table of contents for their favorite germ. The book is heavy and expensive and as is true with standard textbooks will need frequent revision to keep the material current. In my opinion this book would have been much better presented in a lighter, less expensive softback form.

RICHARD LEONARDS, MD

AUTHOR INDEX

Abrams, David E., Los Angeles 157
Adams, Thompson, Los Angeles 163
Afonso, Jose F., Hayward 17
Ames, Adelbert III, Boston 38
Anderson, Fred M., Reno 487
Anthony, Bascom F., Torrance 456, 458
Asbury, Arthur K, San Francisco 153
Ashley, Edd J., Loma Linda 500
Atkinson, Leslie, La Jolla 174

Baker, Lynn F., Natal, Durban, South Africa 252
Balzer, Reuben J., Walnut Creek 328
Barbour, Benjamin H., Los Angeles 157
Barnett, Thomas E., Los Angeles 282
Baxter, John D., San Francisco 301
Becker, Charles E., San Francisco 183, 328
Benson, Larry E., La Jolla 410
Bernard, J. David, Stockton 247
Berne, Thomas V., Los Angeles 157
Bick, Rodger L., Bakersfield 163
Blahd, W. H., Los Angeles 491
Blaisdell, F. William,
San Francisco 92, 252, 334, 421, 502
Blau, Leslie, Los Angeles 353
Bleck, Eugene E., Hillsborough, CA 77
Boerner, Udo, San Francisco 183
Boylen, Thomas C., Los Angeles 8
Brenner, Barry M., San Francisco 33
Brotman, Martin, San Francisco 392
Buchta, Richard M., San Diego 55
Buscaglia, Lucian, Stockton 317

Campbell, Charles G., La Jolla 448
Chapman, Michael, San Francisco 421
Chiapella, Karl J., Chico 500
Cleveland, Richard J., Torrance 412
Cloninger, Paul, Irvine 322
Cohn, Roy, Stanford 1
Conant, Marcus A., San Francisco 46
Condy, Mercy, Stanford 1
Connor, James D., San Diego 55
Coskey, Richard L., Sherman Oaks 319
Costanza, David J., San Francisco 77
Coulson, Alan S., Stanford 1

Dabbert, Olgard, San Diego 250
Danzig, Ronald, Sherman Oaks 319
Deem, Michael A., Washington, D.C. 105
DeGenaro, Frank, Jr., San Diego 55
Dollinger, Malin R., Torrance 412
Dreyfus, Pierre M., Davis 161
Drutz, David J., San Antonio 485
Dua, Sohan Lal, Sacramento 167

Edwards, William M., Carson City 507
Empey, Lucas W., Sacramento 500
Engleman, Edgar G., San Francisco 95
Epstein, Ervin, Oakland 497

Felch, William C., Rye, NY 167
Fiala, Milan, Torrance 369
Fisk, Norman M., Palo Alto 386
Fletcher, Mary Ann, San Diego 55
Fox, Leon Parrish, San Jose 189
Franco, Jorge A., San Jose 419
Franklin, Bruce, Los Angeles 200
Friedland, Gerald W., Stanford 110
Friedman, William F., San Diego 315
Fuller, Scott, La Jolla 174

Galant, Stanley P., Irvine 463
Gerner, Robert, La Jolla 376
Giampaoli, Albert V., San Jose 326
Gitnick, Gary L., Los Angeles 241
Gold, Eli, Jamaica, West Indies 407
Gold, Warren M., San Francisco 489
Gottlieb, Leon S., Los Angeles 8
Granger, Gayle A., Irvine 322
Greenberg, Lawrence M., Davis 105
Greenberg, Lowell H., Torrance 412

Hale, Meredith S., Panorama City 74
Hantman, David I., Los Angeles 241
Hawkins, Donald B., Los Angeles 282, 300
Heidbreder, G. A., Los Angeles 116
Hoffman, Julien I. E., London 315
Hopkins, G. Bruce, La Jolla 448
Hogness, John R., Washington, D.C. 88
Holt, Steve A., Stanford 110
Hunt, Thomas K., San Francisco 250

Imagawa, David T., Torrance 369

Jagger, Paul I., San Diego 348
Jamison, Rex L., Stanford 205
Jonsen, Albert R., San Francisco 169
Judd, Lewis, La Jolla 376

Kadin, Michael R., Pasadena 193
Kasper, Carol K., Los Angeles 273
Kent, Leon, Los Angeles 353
Keys, Thomas F., Los Angeles 72, 452, 459
Klock, John C., San Francisco 183
Kovaleski, Bernadine, San Jose 419
Krishnamurthy, G. T., Los Angeles 491
Kristensen, Kai A. B., La Jolla 448

Lee, Philip R., San Francisco 430
Lewin, Andrew J., Los Angeles 27, 328
Lim, Robert C., Jr., San Francisco 92
Lippmann, Maurice, Torrance 412
Lipshin, Jack, Panorama City 74
Looney, Gerald L., Los Angeles 78
Louie, James S., Torrance 458
Lowther, Laura, Los Angeles 116
Lucas, Zoltan J., Stanford 1
Lund, Harold G., Torrance 412

Madden, Sidney C., Los Angeles 241
Maddox, David A., San Francisco 33
Mahler, Richard J., Duarte, CA 358
Mandell, Arnold, La Jolla 376
Manning, Phil R., Los Angeles 416
McCullough, David L., La Jolla 410
McMahon, Shirley A., Marblehead, Mass 105
McNamara, John J., Jamaica, NY 263
Mendoza, Guillermo, San Diego 124
Mercer, Paul F., London, Ontario 33
Mestman, Jorge H., Los Angeles 416
Miller, Alden H., Los Angeles 300
Millman, Stephen, La Jolla 376
Minkowski, William L., Los Angeles 116
Moore, Francis D., Boston 79

Nickel, Vernon L., Loma Linda 500
Nicoloff, John T., Los Angeles 416
Novey, Harold S., Irvine 322
Nyhan, William L., San Diego 55

Ogden, Wendell, San Bernardino 329
Owsley, John Q., Jr., San Francisco 101

Palmer, Edward, Lake Oswego, OR 419
Palmer, John M., Davis 363
Parton, Lance, Los Angeles 273
Parzen, Zane, La Jolla 376
Pasternak, D. P., Burlingame 244
Pennington, Merle, Tualatin, OR 80
Petit, Donald W., Pasadena 167
Pitlick, Paul T., San Diego 315
Plum, Fred, New York City 152
Prichard, Lorraine, La Jolla 174

Rankin, Thomas J., Orange 441
Rapaport, Samuel I., Los Angeles 239, 513
Ratnoff, Oscar D., San Francisco 226
Renz, Lowell E., Carmichael, CA 251
Reynolds, Michael, Orange 441
Riggs, Mary, Los Altos 249
Rodman, Howard D., Panorama City 74
Root, Irving, San Bernardino 329
Rosenberg, Roger N., San Diego 124

Sadler, Russell B., San Bernardino 328
Samson, Paul C., Oakland 251
Sanazaro, Paul J., Washington, D.C. 344
Sanfelippo, Mary Lu, La Jolla 410
Schmida, Thomas O., Santa Cruz 77
Schneiderman, Lawrence J., La Jolla 174
Schrier, Monika, San Jose 419
Scott, Robert T., San Francisco 131
Scott, Wayne, San Bernardino 329
Seltzer, David C., Los Angeles 282
Senter, Thomas P., Davis 161
Shearn, Martin A., San Francisco 247
Sheldon, George F., San Francisco 334
Shinefield, Henry R., San Francisco 67
Shonick, Helen, Los Angeles 116
Shulman, Alex. G., Beverly Hills 278
Silcott, Robert B., Los Angeles 157
Silvergleid, Arthur J., Stanford 239
Singer, Peter A., Los Angeles 416
Smith, Roger G., Hillsboro, OR 249
Specht, Elmer E., San Francisco 287
Stein, Michel D., Campbell, CA 327
St. Geme, Joseph W., Jr., Torrance 369
Stevens, David A., San Jose 267
Stites, Daniel, San Fancisco 471
Stoller, Robert, Los Angeles 376
Stoneman, George B., Los Angeles 282

Terry, R., Los Angeles 157
Thompson, Ronald W., Los Angeles 193
Thrupp, Lauri D., Irvine 322
Tong, Theodore G., San Francisco 328
Trunkey, Donald D.,
San Francisco 92, 252, 334, 421, 502
Tuxen, Peter, Stockton 317

Ulmer, David D., Los Angeles 200

Vanags, Klitia, San Jose 419

Ward, Paul D., Oakland 425
Weinberg, David L., San Bruno 326
Weiss, Robert C., Los Angeles 116
Weller, William J., San Jose 189
Westin, G. Wilbur, Los Angeles 314
White, Kerr L., Baltimore 338
Wilder, Helen, San Jose 189
Wilson, Archie F., Irvine 463
Wilson, Thelma, Portland 255

Yoshimori, Robert N., Torrance 456

IN MEMORIAM

Allen, James Stratford, Feb 28, 1974 518
Allison, Harry B., Apr 16, 1974 518
Arnot, Philip Howard, Jan 25, 1974 352
Athanasiou, Athanasios, Mar 13, 1974 518
Azevedo, John Anthony, Oct 24, 1973 181
Beal, Philip Gowans, Oct 12, 1973 181
Beggs, James Henry, Dec 12, 1973 518
Bennett, Everett E., Mar 21, 1974 518
Berlin, Anthony S., Dec 7, 1973 518
Biben, Robert Leslie, Dec 4, 1973 181
Bridgman, Olga, Feb 6, 1974 518
Bristow, David Austin, Dec 6, 1973 181
Burch, John Thomas, Mar 24, 1974 518
Burket, Joseph Arthur, Jan 27, 1974 352
Butler, George A., Feb 21, 1974 518
Cabrera, Eusebio Emmanuel, Mar 30, 1974 518
Canon, Lawrence S., Nov 16, 1973 181
Conry, Robert Francis, Jan 19, 1974 352
Crockett, Herbert Gillis, Feb 22, 1974 518
Cunningham, James Emery, Feb 10, 1974 352
Cushman, Glenn F., Feb 16, 1974 352
Deeb, Paul H., Mar 2, 1974 518
Dillon, Richard, Jan 8, 1974 271
Eiler, John Oliver, Oct 30, 1973 181
Ellis, Grant, Feb 12, 1974 352
Erickson, Elenore J., Feb 25, 1974 440
Fiscus, William Patrick, Feb 27, 1974 440
Fitzgerald, William J., Nov 21, 1973 181
Fraser, Alexander Falconer, Mar 9, 1974 440
Friedman, Henry Tauber, Jan 22, 1974 440
Gaspard, Frederic Joseph, Mar 19, 1974 440
Geyser, Harry A., Nov 17, 1973 181

Gonzalez, Luis Guerrero, Nov 3, 1973 440
Greenberg, Alfred, Apr 14, 1974 518
Greig, Kennett A., Feb 25, 1974 440
Grieco, Sebastian C., Mar 24, 1974 518
Hale, Donald E., Nov 9, 1973 518
Hall, Cameron B., Jan 20, 1974 352
Hammel, Max Arthur, Jan 12, 1974 271
Handelman, Jack H., Jan 6, 1974 271
Harrison, Charles William, Jr., Mar 24, 1974 518
Hartman, Deane Clemens, Sep 2, 1973 181
Hedberg, Caleb Clifford, Mar 15, 1974 440
Hoag, Harry James, Sr., Feb 6, 1974 352
Holmes, Olin Monroe, Feb 9, 1974 352
Howard, Lot D., Jr., Feb 25, 1974 352
Irwin, Ralph L., Apr 4, 1974 519
Kaufman, Bernard, Sr., Nov 18, 1973 181
Kavinoky, Nadina R., Nov 24, 1973 519
Kaye, Van Walter, Mar 2, 1974 440
Keate, Wendell Snow, Jan 3, 1974 271
Keller, Florence, Jan 15, 1974 440
Koefod, Hilmar Olaf, Feb 12, 1974 352
Koppelman, Harold, Oct 24, 1973 181
Korostoff, Bernard, Jan 3, 1974 352
Krugmeier, Carl E., Sep 22, 1973 352
Lasin, Harry, Mar 28, 1974 519
Latini, John Julio, Feb 21, 1974 352
Lehman, Robert G., Jan 1, 1974 271
Leik, Donald William, Dec 26, 1973 271
Lenahan, George T., Feb 15, 1974 352
Levy, Marvin Shephard, Dec 24, 1973 271
Libby, Robert Green, Feb 25, 1974 440
Loseoff, Theodore Allan, Feb 23, 1974 519
MacKay, Eaton MacLeod, Oct 30, 1973 181
Maddox, Robert C., Jan 3, 1974 271
Mand, Louise Auerbach, Apr 21, 1974 519
Mankinen, Carl J., Nov 17, 1973 181
Martin, Charles George, Feb 8, 1974 440
Matt, Wayland P., Feb 28, 1974 440
McClure, Gillian M., Nov 28, 1973 181
Mollath, August L., Dec 28, 1973 271
Moore, Harold M., Dec 15, 1973 271
Morris, David Lawrence, Jan 1, 1974 271
Murphy, William Henry, Nov 21, 1973 181
Neilsen, Melvin L., Jan 10, 1974 271
Nesselrod, Jerrold P., Apr 10, 1974 519
Oakleaf, Donovan Carl, Jan 3, 1974 271
Olesky, Elmer, Nov 23, 1973 181
Page, Warren E., Dec 1, 1973 181
Payne, Ross A., Mar 5, 1974 519
Pendleton, Walter R., Nov 18, 1973 182
Person, Edward C., Jan 24, 1974 271
Quickert, Marvin H., Mar 23, 1974 440
Ransom, Charles Herman, Oct 23, 1973 182
Reamer, William Leslie, Jan 23, 1974 440
Roach, Francis Xavier, Jr., Mar 11, 1974 519
Rook, Francis L., Dec 25, 1973 271
Root, Herbert Blanchard, Nov 16, 1973 182
Ross, Peter, Jan 22, 1974 352
Scherb, Robert Emmett, Jan 11, 1974 271
Schmitt, George Donald, Apr 11, 1974 519
Schwartz, George, Nov 29, 1973 272
Scott, Walter, Jan 25, 1974 352
Sicherman, Karl L., Feb 22, 1974 519
Sirbu, Abraham B., Jan 12, 1974 272
Sorensen, Roy W., Jan 24, 1974 272
Spencer, Frank A., Nov 28, 1973 182
Stahl, Vernon O., Nov 24, 1973 182
Stephens, Lorin L., Mar 24, 1974 519
Strickler, John P., Jan 8, 1974 272
Sweedler, Daniel Robert, Mar 17, 1974 519
Talbot, Harry F., Jr., Mar 16, 1974 519
Thomas, John Merrill, Dec 6, 1973 182
Townsend, Ernest Will, Feb 18, 1974 440
Veldee, Milton Victor, Jan 15, 1974 272
Wagner, Claude F., Feb 21, 1974 440
Ward, John H., Jr., Nov 24, 1973 182
Werlinich, Michael, Nov 15, 1973 182
Wilbur, Blake C., Mar 10, 1974 440
Wilson, Ethelbert R., Mar 20, 1974 440
Wiper, Thomas Benedict, Jan 31, 1974 352
Wood, Elden Glenn, Dec 29, 1973 272
Wood, Laurin L., Mar 31, 1974 519
Yumibe, Toshio, Feb 3, 1974 440

SUBJECT INDEX

A

Abdominal Injury, Blunt, see *Indications for Laparotomy*
Abdominal Wounds, see *Penetrating*
Abortion, see *Birth Control*
Abuse, see *Drug*
Access to Medical Care as a Citizen's Right—Position Paper by CMA Committee on Role of Medicine in Society, and House of Delegates 438
Acupuncture (Letter to Editor), Reuben J. Balzer . 328
Reply, Andrew J. Lewin 328
Acupuncture and the Law (Letter to Editor), Gerald L. Looney 78
Acupuncture and Its Role in Modern Medicine, Andrew J. Lewin 27
Letter to Editor, Reuben J. Balzer 328
Acupuncture in Nevada (Government and Medicine), William M. Edwards, Jr. 507
Editorial, Fred M. Anderson 487
Acute Cerebellar Ataxia of Childhood—An Unusual Case of Varicella, Pierre M. Dreyfus and Thomas P. Senter 161
Adenoviral Infections, see *Potpourri of*
Adenovirus, see *Ubiquitous*
Adolescents, see *Family Planning Services for*
Aggeler, Paul M., Memorial Lecture, See *Hemophilia*
Airway Obstruction in the Newborn (Page-End), Alden H. Miller and Donald B. Hawkins 300
Alcoholism, CMA Committee on, see *Practical Criteria for Diagnosis*
Aldosteronism, see *Suppressed Plasma*
American Heart Association, see *Clinical Cardiology*
Anesthesia in a Community Hospital, see *Obstetrical Caudal*
Ankylosing Spondylitis, see *Diagnosis of "Rheumatoid Variants"*

Antacid Induction of Phosphate Depletion Syndrome in Renal Failure, David E. Abrams, Robert B. Silcott, R. Terry, Thomas V. Berne, and Benjamin H. Barbour 157
Antibiotic Excretion in Unilateral Structural Pyelonephritis, see *Differential*
Antibiotic Resistance, see *Gonococcal*
Antigen, Hepatitis B, see *Irradication of*
Antiparasitic Drugs, see *Hard to Find*
Arachnodactyly, see *Congenital*
Are Carrots and Sticks for Donkeys or for Doctors? (Editorial) 277
Letter to Editor, Edward Palmer 419
Artery Injury, see *Hepatic*
Arthritides, see *Diagnosis of "Rheumatoid Variants"*
Arthritis, see *Immunotherapy*
Asthma, see *Recent Advances*
Ataxia, see *Acute Cerebellar*
Attitudes Toward Women Physicians—A Study of 500 Clinic Patients, Edgar G. Engleman 95
Augmentation Mammaplasty, see *Camouflage and*

B

"Backlash"—A Correction (Letter to Editor), Francis D. Moore 79
Biological Uniqueness and Quality of Life (Editorial) 315
Birth Control, Sterilization and Abortion—Attitudes of Catholic and Protestant Clergymen in San Diego Toward Use in Families with Genetic Illness (Controversial Ethical Issues), Lawrence W. Schneiderman, Lorraine Prichard, Scott Fuller, and Leslie Atkinson 174
Bleeding Associated with Massive LSD Overdose, see *Coma, Hyperthermia*

Book Reviews:
Dermal Pathology, *Graham et al* 180
Diseases of the Vulva, *Janovski & Douglas* 350
Embryology for Surgeons, Gray & Skandalakis 520
Heritable Disorders of Connective Tissue—4th Ed., *McKusick* 351
Hereditary Retinal and Choroidal Diseases—Vol I: Evaluation, *Krill* 350
Infectious Diseases, Hoeprich 520
Infectious Diseases of Children and Adults—5th Ed., *Krugman & Ward* 270
Jack Sprat Cookbook, The, *Zane* 350
Licit and Illicit Drugs, *Brecher* 180
Minimal Cerebral Dysfunction in Children, *Walzer & Wolff* 270
Neonatal Heart Disease, *Friedman et al* 351
Pathology of the Cerebral Blood Vessels, *Stehbens* 351
Radiologic Examination of the Urinary Tract, *Pollack* 270
Vesicoureteral Reflux and Pyelonephritis, *Hutch & Amar* 351

Bran Revisited (Letter to Editor), Lucas W. Empey 500
Bronchoscopy, see *Rigid Tube*

C

California Medical Association:
Access to Medical Care as a Citizen's Right (Committee on Role of Medicine in Society and House of Delegates Position Paper) 438
Practical Criteria for the Diagnosis of Alcoholism in Hospital Practice (Committee on Alcoholism and Other Drug Dependence, Scientific Board and House of Delegates) 438

Camouflage and the Augmentation Mammaplasty, John Q. Owsley, Jr. 101
Carcinoid Heart Disease, see *Tricuspid Valve Replacement*
Cardiac Arrest due to Extreme Tachycardia with Wolff-Parkinson-White Syndrome, Richard L. Coskey and Ronald Danzig 319
Cardiology, see *Clinical*
Catholic, see *Birth Control*
Caudal Anesthesia, see *Obstetrical*
Caveats for PSRO's, Kerr L. White 338
Editorial 314
Cellular Swelling, see *Role of*
Cerebellar Ataxia, see *Acute*
Childhood Ataxia, see *Acute Cerebellar Ataxia*
Children, Hyperactive, see *Side Effects of Dextroamphetamine*
China, see *Medicine and Public Health in the People's Republic of*
[Chinese Medicine], see *Acupuncture in Nevada*
Chinese Women, see *Histiocytic Medullary Reticulosis*
Cigarette Smoking Ten Years Later (Editorial) ... 70
Clergymen, see *Birth Control*
Clinical Features [of] Enterocolitis, see *Neonatal*

Clinical Cardiology—American Heart Association:
Suppressed Plasma Renin Activity and Primary Aldosteronism, Paul I. Jagger 348

Clinical Medicine, Important Advances in, see *Epitomes*
Clinical Pharmacists and Patient Care (Letter to Editor), Theodore G. Tong and Charles E. Becker 328
Cluster Headaches—A New Treatment (Letter to Editor), Albert V. Giampaoli 326
Coccidioidal Osteomyelitis, see *Immunotherapy*
Cocaine Abuse (Page End), Louis Jolyon West 294
Colon, see *High Bulk Diet*
Coma, see *Metabolic*
Coma, Hyperthermia and Bleeding Associated with Massive LSD Overdose—A Report of Eight Cases, John C. Klock, Udo Boerner and Charles E. Becker 183
Committee on Alcoholism, see *Practical Criteria*
Committee on Role of Medicine in Society, see *Access to Medical Care*
Competence, Professional, see *Concerning*
Concerning Professional Competence (Letter to Editor), Donald W. Petit 167
Author Replies, The, William C. Felch 167
Congenital Contractural Arachnodactyly, Meredith S. Hale, Howard D. Rodman and Jack Lipshin 74
Conservative and Surgical Aspects of Disc Lesion Management—Follow-Up Review of 244 Cases, Leslie Blau and Leon Kent 353
Continuing Education Program, see *OMA's*
[Continuing Medical Education], see *Concerning Professional Competence*
Continuing Medical Education, Mandatory, see *Review of*

Controversial Ethical Issues:
Birth Control, Sterilization and Abortion—Attitudes of Catholic and Protestant Clergymen in San Diego Toward Use in Families with Genetic Illness, Lawrence J. Schneiderman, Lorraine Prichard, Scott Fuller, and Leslie Atkinson 174

Coxa Plana (Legg-Perthes Disease), (Medical Progress), Elmer E. Specht 287
Editorial, G. Wilbur Westin 314
Curious Odyssey of Regional Medical Programs, The (Government and Medicine), Paul D. Ward 425
Current Concepts of Sodium Chloride and Water Transport by the Mammalian Nephron (Medical Progress), Paul F. Mercer, David A. Maddox and Barry M. Brenner 33
Cushing's Syndrome, see *Iatrogenic*
Cytomegalovirus Disease, see *Forty Day Fever*

D

Death from Ischemia (Editorial), Adelbert Ames III 238
Dextroamphetamine Therapy, see *Side Effects of*
Dextroamphetamine Therapy in Hyperactive Children (Letter to Editor), Michel D. Stein 327
Diabetic Ketoacidosis, see *Hemochromatosis*
Diabetes Mellitus—Distinguishing Between Patients Receiving Insulin and Those Requiring Insulin Therapy, Richard J. Mahler 358
Diabetic Rehabilitation Center (Information) 349
Diagnosis of Alcoholism, see *Practical*
Diagnosis of "Rheumatoid Variants"—Ankylosing Spondylitis, the Arthritides of Gastrointestinal Diseases and Psoriasis, and Reiter's Syndrome, Michael D. Reynolds and Thomas J. Rankin 441
Differential Antibiotic Excretion in Unilateral Structural Pyelonephritis, John M. Palmer 363
Disc Lesion Management, see *Conservative and Surgical Aspects of*
Diverticular Disease, see *High Bulk Diet for*
[Drug Abuse], see *Cocaine*
Drug Abuse, see *Pulmonary Complications of*
Drug Abuse, see *Sternal-Costal Infection*
Drugs, Antiparasitic, see *Hard to Find*

E

Early and Periodic Screening, Medi-Screen Program Structure and Standard Setting (Government and Medicine), John J. McNamara 263
Electromyography, see *On the Performance of*
Emergency Medicine (Editorial) 91
Enterocolitis, see *Neonatal*

Epitomes of Progress in Clinical Medicine:
Otolaryngology 62
Radiology 143
Ophthalmology 233
Psychiatry 307
Pediatrics 400
Neurology 476

Ethic, see *New*

Editorial Comment:
Male Transsexualism—Gender Dysphoria Syndrome —The Conceptualization that Liberalizes Indications for Total Gender Reorientation and Implies a Broadly Based Multi-Dimensional Rehabilitative Regimen, Norman M. Fisk 386

Editorials:
Are Carrots and Sticks for Donkeys or for Doctors [Politics and National Health Care] 237
Letter to Editor, Edward Palmer 419
Biological Uniqueness and the Quality of Life 315
Cigarette Smoking Ten Years Later 70
Death from Ischemia, Adelbert Ames III 238
Emergency Medicine 71
Idiopathic Polyneuritis, Arthur K. Asbury 153
Immunity to Reinfection in Patients with Gonorrhea, David J. Drutz 485
Instant Acupuncture for Nevada, Fred M. Anderson 487
Legg-Calvé-Perthes, G. Wilbur Westin 314
More on PSRO's 314
Male Transsexualism—Gender Dysphoria Syndrome —The Conceptualization that Liberalizes Indications for Total Gender Reorientation and Implies a Broadly Based Multi-Dimensional Rehabilitative Regimen, Norman M. Fisk 386
National Health Insurance—Are We Really Ready for It Yet? 408
Correction 490
On Justice in Medical Care 156
PSRO—Update 1974 155
Recent Advances in the Pathophysiology of Asthma, Warren M. Gold 489
Rule of Wal 484
"Trauma Rounds" 240
Treatment of Ventricular Septal Defect, Julien I. E. Hoffman 315
Ubiquitous Adenovirus, The, Henry R. Shinefield .. 67
Unconscious Patient, The, Fred Plum 152
Venous Thrombosis—Newer Diagnostic and Therapeutic Approaches, Samuel I. Rapaport 239
Letter to Editor, Jorge Franco, et al 419
Viral Infection of the Fetus, Eli Gold 407
Voice for Medicine in the West 67

Endotracheal Tube Perforation of the Hypopharynx, Donald B. Hawkins, David C. Seltzer, Thomas E. Barnett and George B. Stoneman 282

F

Family Planning Services for Adolescents and Young Adults, William L. Minkowski, Robert C. Weiss, Laura Lowther, Helen Shonick and G. A. Heidbreder 116
Fetus, see *Viral Infections of the*
Forty Day Fever—An Epidemic of Cytomegalovirus Disease in a Renal Transplant Population, Alan S. Coulson, Zoltan J. Lucas, Mercy Condy and Roy Cohn 1
Functional Recovery in Older Patients after Prolonged Oliguria, Mary Lu Sanfelippo, Larry E. Benson and David L. McCullough 410

G

Gender Dysphoria Syndrome, see *Male Transsexualism*
Genetic Illness, see *Birth Control*
Gonococcal Antibiotic Resistance in Los Angeles, Thomas F. Keys 452

Gonococcal Infections—Laboratory, Clinical and Epidemiological Aspects (UC, Los Angeles, and Harbor General Hospital Teaching Conference), Moderator: Bascom F. Anthony 456
Laboratory Diagnosis of Neisseria Gonorrhoeae, Robert N. Yoshimori 456
Extra-Genital Manifestations of Gonococcal Disease, James S. Louie 458
Pediatric Aspects of Gonococcal Disease, Bascom F. Anthony 458
Epidemiology and Management of Gonorrhea, Thomas F. Keys 459
Editorial, David J. Drutz 485
Gonorrhea, see *Immunity to Reinfection*

Government and Medicine:

Early and Periodic Screening, Medi-Screen Program Structure and Standard Setting, John J. McNamara 263
Curious Odyssey of Regional Medical Programs, The, Paul D. Ward 425
Acupuncture in Nevada, William M. Edwards, Jr. .. 507
Editorial, Fred M. Anderson 487

H

Harbor General Hospital, see *Specialty Conferences*
Hard to Find Antiparasitic Drugs—Drugs Available from the Parasitic Disease Drug Service (Page End) 391
Headaches, see *Cluster*
Health and Medicine, see *Makings of Policy*
Health Care, National, see *Are Carrots and Sticks*
Health Care Crisis, see *Traumatic Injury*
Health Insurance, see *National*
Heart Disease, see *Tricuspid Valve Replacement*
Hemlock, see *Poison*
Hemochromatosis Presenting as Diabetic Ketoacidosis with Extreme Hyperglycemia, D. P. Pasternak 244
Hemophilia, see *Reproduction*
Hemophilia and von Willebrand's Disease—Fourth Annual Paul M. Aggeler Memorial Lecture (Medical Staff Conference) 226
Hepatic Artery Injury in Non-Penetrating Trauma, Peter Tuxen and Lucian Buscaglia 317
Hepatitis, Chronic, see *Problem of Diagnosis and Classification of*
Hepatitis B Antigen, see *Irradication of*
High Bulk Diet for Diverticular Disease of the Colon, Alex. G. Shulman 278
Letter to Editor, Lucas W. Empey 500
Histiocytic Medullary Reticulosis in Two Chinese Women, Rodger L. Bick and Thompson Adams . 163
Hodgkin's Disease, see *Lymphangiography*
Hospital Infection Control, see *Infection*
House of Delegates, see *Access to Medical Care*
Human Infection with Vibrio Fetus, Bruce Franklin and David D. Ulmer 200
Hyperactive Children, see *Side Effects of Dextroamphetamine*
Hyperalimentation in Patients with Multiple Injuries, see *Role of*
Hyperglycemia, see *Hemochromatosis*
Hyperthermia, see *Coma*
Hyperthyroidism in the Presence of Panhypopituitarism—Thyroid Crisis and Hypothyroidism Following Radioiodine Treatment, G. T. Krishnamurthy and W. H. Blahd 491
Hypoglycemia in Renal Disease (Letter to Editor), Sohan Lal Dua 167
Hypopharynx, see *Endotracheal Tube*
Hypothalamic-Hypothyroidism Secondary to Sheehan's Syndrome, Peter A. Singer, Jorge H. Mestman, Phil R. Manning and John T. Nicoloff 416
Hypothyroidism, see *Hyperthyroidism*

I

Iatrogenic Cushing's Syndrome (Medical Staff Conference) 301
Idiopathic Acute Symmetrical Polyradiculoneuritis —The Landry-Guillain-Barré-Strohl Syndrome (UC, San Diego, and University Hospital of San Diego County), Participants: Roger N. Rosenberg and Guillermo Mendoza 124
Editorial, Arthur K. Asbury 153
Idiopathic Polyneuritis (Editorial), Arthur K. Asbury 153
Immunity to Reinfection in Patients with Gonorrhea (Editorial), David J. Drutz 485
Immunoglobulin Deficiency Disorders (Medical Staff Conference) 471
Immunotherapy with Transfer Factor in Disseminated Coccidioidal Osteomyelitis and Arthritis, Paul Cloninger, Lauri D. Thrupp, Gale A. Granger and Harold S. Novey 322
Important Advances in Clinical Medicine, see *Epitomes*
Indications for Laparotomy Following Blunt Abdominal Injury (Trauma Rounds—San Francisco General Hospital), Chief Discussant: F. William Blaisdell 502
Infancy, see *Ventricular Septal Defect in*
Infection, see *Sternal-Costal*
Infection Control in the Hospital [Santa Clara Valley Valley Medical Center]—A Report on Workshop Discussions (Notes from Important or Unusual Meetings), David A. Stevens 267
Infections, see *Viral*
Infections, Adenoviral, see *Potpourri of*

Information:

American Heart Association, see *Clinical Cardiology*
Diabetic Rehabilitation Center 349

Informed Consent (Letter to Editor), Russell B. Sadler 328

Informed Opinion:

PSRO and Options for the Future, Paul J. Sanazaro 344
Editorial 314
(See also *Caveats for PSRO's, Kerr L. White* .. 348)
Research in Medical Schools—A Personal View, Samuel I. Rapaport 513

Instant Acupuncture for Nevada (Editorial), Fred M. Anderson 487
Institute of Medicine, see *Makings of Policy*
[Insurance Claim Processing], see *Some Order from Chaos*
Insulin, see *Diabetes Mellitus—Distinguishing Between Patients Receiving*
Insurance, see *National*
Irradication of Hepatitis B Antigen in Fulminant Hepatitis, Gary L. Gitnick, David I. Hantman and Sidney C. Madden 241
Ischemia, see *Death from*

K

Ketoacidosis, see *Hemochromatosis*

L

Landry-Guillain-Barré-Strohl Syndrome, see *Idiopathic, Acute, Symmetrical Polyradiculoneuritis*
Laparotomy, see *Indications for*
Law, see *Acupuncture*
Legg-Calvé-Perthes (Editorial), G. Wilbur Westin . 314
Legg-Perthes Disease, see *Coxa Plana*

Letters to Editor:

Acupuncture, Reuben J. Balzer 328
Reply, Andrew J. Lewin 328
Acupuncture and the Law, Gerald L. Looney 78
"Backlash"—A Correction, Francis D. Moore 79
Bran Revisited, Lucas W. Empey 500
Clinical Pharmacists and Patient Care, Theodore G. Tong and Charles E. Becker 328
Cluster Headaches—A New Treatment, Albert V. Giampaoli 326
Concerning Professional Competence, Donald W. Petit 167
Author Replies, William C. Felch 167
Dextroamphetamine Therapy in Hyperactive Children, Michel D. Stein 327
Hypoglycemia in Renal Disease, Sohan Lal Dua .. 167
Informed Consent, Russell B. Sadler 328
Malpractice Awards, Olgard Dabbert 250
Of Maturity in Medical Practice, Edward Palmer .. 419
OMA's Continuing Education Program, Mary Riggs and Roger G. Smith 249
On the Performance of Electomyography, Vernon L. Nickel and Edd J. Ashley 500
"Open Book" Recertification Examination, An, David L. Weinberg 326
Poison Hemlock [Water Hemlock], Thomas O. Schmida 77
Reply, David J. Costanza 78
Rigid Tube Bronchoscopy, Paul C. Samson 251
Reply, Lowell E. Renz 251
Some Order from Chaos, Eugene E. Bleck 77
Thermography in Venous Thrombosis, Jorge A. Franco, Bernadine Kovaleski, Klitia Vanags, Monika Schrier 419
Traumatic Injury—A Health Care Crisis, Thomas K. Hunt 250
Verminous Ophthalmia, Karl J. Chiapella 500

LSD Overdose, see *Coma, Hyperthermia*
Lymphangiography—Its Practical Value in Surgically Staged Patients with Hodgkin's Disease, Michael R. Kadin and Ronald W. Thompson ... 193

M

Makings of Policy for Medicine and Health—A Report on the Institute of Medicine (Special Article), John R. Hogness 88
Male Transsexualism (UC, San Diego, and San Diego Veterans Administration Hospital, Psychiatric Grand Rounds), Participants: Robert Gerner, Lewis Judd, Arnold Mandell, Stephen Millman, Zane Parzen and Robert Stoller 376
Editorial Comment, Norman M. Fisk 386
Male Transsexualism—Gender Dysphoria Syndrome —The Conceptualization that Liberalizes Indications for Total Gender Reorientation and Implies a Broadly Based Multi-Dimensional Rehabilitative Regimen (Editorial Comment), Norman M. Fisk 386
Malpractice Awards (Letter to Editor), Olgard Dabbert 250
Mammalian Nephron, see *Current Concepts Sodium Chloride*
Mammaplasty, Augmentation, see *Camouflage and*
Management of Pelvic Fractures (Trauma Rounds —San Francisco General Hospital), Chief Discussant: Michael Chapman 421
Medical Care, see *Access to*
Medical Care, see *On Justice in*
Medical Investigation of Alleged Rape, The (Special Article), Irving Root, Wendell Ogden and Wayne Scott 329
Medical Practice, see *On Maturity in*

Medical Progress:

Current Concepts of Sodium Chloride and Water Transport by the Mammalian Nephron, Paul F. Mercer, David A. Maddox and Barry M. Brenner 33
Role of Cellular Swelling in the Pathogenesis of Organ Ischemia, The, Rex L. Jamison 205
Editorial, Adelbert Ames III 238
Coxa Plana (Legg-Perthes Disease), Elmer E. Specht 287
Editorial, G. Wilbur Westin 314
Recent Advances in the Pathophysiology of Asthma, Archie F. Wilson and Stanley P. Galant 463
Editorial, Warren M. Gold 489

Medical Schools, see *Research in*

Medical Schools of the West:

University of Oregon Medical School 255

Medical Staff Conferences:

Syphilis, Chief Discussant: Marcus A. Conant ... 46
Metabolic Coma, Chief Discussant: Robert T. Scott 131
Editorial, Fred Plum 152
Hemophilia and von Willebrand's Disease—4th Annual Paul M. Aggeler Memorial Lecture, Chief Discussant: Oscar D. Ratoff 226
Iatrogenic Cushing's Syndrome, Chief Discussant: John D. Baxter 301
Problem of Diagnosis and Classification of Chronic Hepatitis, Chief Discussant: Martin Brotman ... 392
Immunoglobulin Deficiency Disorders, Chief Discussant: Daniel Stites 471

Medicine, see *Acupuncture*
Medicine, see *Emergency*
Medicine, see *New Ethic*
Medicine, see *Voice for*
Medicine, Institute of, see *Makings of Policy*
Medicine and Health, see *Makings of Policy*
Medicine and Public Health in the People's Republic of China—Observations and Reflections of a Recent Visitor, Philip R. Lee 430

Medicine in Society:

Access to Medical Care as a Citizen's Right (Committee on Role of Medicine in Society and House of Delegates Position Paper) 438

Practical Criteria for the Diagnosis of Alcoholism in Hospital Practice (Committee on Alcoholism and Other Drug Dependence, Scientific Board, and House of Delegates) 438

Medi-Screen Program, see *Early and Periodic*
Mesodermal Tumors, see *Mixed*
Metastatic Tumors, see *Skeletal Scintigraphy*
Metabolic Coma (Medical Staff Conference) 131
Editorial, Fred Plum 152
Minocycline Hydrochloride, see *Treatment of a Cutaneous Nocardia Asteroides Infection with*
Mixed Mesodermal Tumors of the Uterus, Jose F. Afonso 17
More on PSRO's (Editorial) 314

N

National Health Insurance—Are We Really Ready for It Yet? (Editorial) 408
Correction 490
Neonatal Necrotizing Enterocolitis—Clinical and Radiological Features, Steve A. Holt and Gerald W. Friedland 110
Neurology, Important Advances in, see *Epitomes*
Newborn, see *Airway Obstruction in*
New Ethic for Medicine, A (Special Article), Albert R. Jonsen 169
Editorial 156
Nocardia Asteroides Infection, Cutaneous, see *Treatment of*

Notes from Important or Unusual Meetings:

Infection Control in the Hospital [Santa Clara Valley Medical Center]—A Report on Workshop Discussions, David A. Stevens 267

O

Obstetrical Caudal Anesthesia in a Community Hospital—A Satisfactory Plan, Leon Parrish Fox, William J. Weller and Helen Wilder 189
OMA's Continuing Education Program (Letters to Editor), Mary Riggs and Roger G. Smith 249
Of Maturity in Medical Practice (Letter to Editor), Edward Palmer 419
Oliguria, Prolonged, see *Functional Recovery*
On Justice in Medical Care (Editorial) 156
On the Performance of Electromyography (Letter to Editor), Vernon L. Nickel and Edd J. Ashley 500
"Open Book" Recertification Examination, An (Letter to Editor), David L. Weinberg 326
Ophthalmia, see *Verminous*
Ophthalmology, see *Epitomes*
Oregon, see *Review of Mandatory Continuing Medical Education*
[Oregon Medical Association], see *Review of Mandatory Continuing Medical Education*
Organ Ischemia, see *Role of Cellular Swelling*
Osteomyelitis, Disseminated Coccidioidal, see *Immunotherapy*
Otolaryngology, Important Advances in, see *Epitomes*

P

Page Ends:

Airway Obstruction in the Newborn, Alden H. Miller and Donald B. Hawkins 300
Cocaine Abuse, Louis Jolyon West 294
Hard To Find Antiparasitic Drugs Available from the Parasitic Disease Drug Service 391

Panhypopituitarism, see *Hyperthyroidism*
Parasitic Disease Drugs, see *Hard To Find*
Patient Care, see *Clinical Pharmacists*
Paul M. Aggeler Memorial Lecture, Fourth Annual, see *Hemophilia and von Willebrand's Disease*
Pediatrics, Important Advances in, see *Epitomes*
Pelvic Fractures, see *Management of*
Penetrating Abdominal Wounds (Trauma Rounds—San Francisco General Hospital), Chief Discussant: Lynn F. Baker 252
Editorial 240
Pharmacists and Patient Care, see *Clinical*
Phosphate Depletion Syndrome, see *Antacid*
Plasma Renin Activity, see *Suppressed*
Poison Hemlock [Water Hemlock] (Letter to Editor), Thomas O. Schmida 77
Reply, David J. Costanza 78
Policy for Medicine and Health, see *Makings of*
Polyneuritis, see *Idiopathic*
Polyradiculoneuritis, see *Idiopathic, Acute Symmetrical*
Position Papers, see *Statements*
Potpourri of Adenoviral Infections (UC, San Diego, and University Hospital of San Diego County, Pediatric Grand Rounds), Participants: James D. Connor, Richard M. Buchta, Frank DeGenaro, Jr., Mary Ann Fletcher and William L. Nyhan .. 55
Editorial, Henry R. Shinefield 67
Practical Criteria for Diagnosis of Alcoholism in Hospital Practice (CMA Committee on Alcoholism and Other Drug Dependence and Scientific Board) 438
Problem of Diagnosis and Classification of Chronic Hepatitis, The (Medical Staff Conference) 392
Professional Competence, see *Concerning*
Protestant, see *Birth Control*
Pseudomonas, see *Sternal-Costal Infection*
PSRO, see *Caveats for*
PSRO—Update 1974 (Editorial) 155
PSRO and Options for the Future (Informed Opinion), Paul J. Sanazaro 344
Editorial 314
PSRO's, see *More on*

Psychiatric Rounds:

Male Transsexualism (UC, San Diego, and San Diego Veterans Administration Hospital, Psychiatric Grand Rounds), Participants: Robert Gerner, Lewis Judd, Arnold Mandell, Stephen Millman, Zane Parzen and Robert Stoller 376
Editorial Comment, Norman M. Fisk 386

Psychiatry, see *Epitomes*
Psychogenic Pseudo-Sjögren's Syndrome, J. David Bernard and Martin A. Shearn 247
Pulmonary Complications of Drug Abuse, Leon S. Gottlieb and Thomas C. Boylen 8
Public Health in the People's Republic of China, see *Medicine and*
Pyelonephritis, Unilateral Structural, see *Differential Antibiotic Excretion in*

R

Radioiodine Treatment, see *Hyperthyroidism*
Radiological Features [of] Enterocolitis, see *Neonatal*

Radiology, Important Advances in, see *Epitomes*
Rape, Alleged, see *Medical Investigation of*
Recent Advances in the Pathophysiology of Asthma (Medical Progress), Archie F. Wilson and Stanley P. Galant 463
Editorial, Warren M. Gold 489
Recertification Examination, see *"Open Book"*
Regional Medical Programs, see *Odyssey of*
Rehabilitation, see *Diabetic*
Reiter's Syndrome, see *Diagnosis of "Rheumatoid Variants"*
Renal Disease, see *Hypoglycemia in*
Renal Failure, see *Antacid Induction*
[Renal Handling of NaCl and H_2O], see *Current Concepts of Sodium Chloride*
Renal Transplant Population, see *Forty Day Fever*
Renin Activity, see *Suppressed*
Reproduction in Hemophilia, Carol K. Kasper and Lance Parton 273
Research in Medical Schools—A Personal View (Informed Opinion), Samuel I. Rapaport 513
Reticulosis Medullary, see *Histiocytic Medullary*
Review of Mandatory Continuing Education in Oregon (Special Article), Merle Pennington ... 80
Letters to Editor, Mary Riggs and Roger G. Smith 249
Rheumatoid Variants, see *Diagnosis of*
Right, Citizen's, see *Access to Medical Care*
Rigid Tube Bronchoscopy (Letter to Editor), Paul C. Samson 251
Reply, Lowell E. Renz 251
Role of Cellular Swelling in the Pathogenesis of Organ Ischemia, The (Medical Progress), Rex L. Jamison 205
Editorial, Adelbert Ames III 238
Role of Hyperalimentation in Patients with Multiple Injuries, The (Trauma Rounds—San Francisco General Hospital), Chief Discussant: George F. Sheldon 334
Role of Medicine in Society, Committee on, see *Access to Medical Care*
Rule of Wal (Editorial) 484

S

San Diego County, University Hospital of, see *Specialty Conferences*
San Diego Veterans Administration Hospital, see *Psychiatric Rounds*
San Francisco General Hospital, see *Trauma Rounds*
[San Jose Hospital and Health Center], see *Obstetrical Caudal Anesthesia*
[Santa Clara Valley Medical Center], see *Notes from Important or Unusual Meetings*
Scientific Board, CMA, see *Practical Criteria for Diagnosis of Alcoholism*
Scintigraphy, see *Skeletal*
Screening, see *Early and Periodic*
Septal Defect, see *Ventricular*
Sheehan's Syndrome, see *Hypothalamic-Hypothyroidism Secondary to*
Sjögren's Syndrome, see *Psychogenic Pseudo*
Skeletal Scintigraphy—The Use of Technetium 99M-Labeled Complexes in the Detection of Early Osseous Involvement by Metastatic Tumors, G. Bruce Hopkins, Kai A. B. Kristensen and Charles G. Campbell 448
Smoking, see *Cigarette*
Side Effects of Dextroamphetamine Therapy of Hyperactive Children, Lawrence M. Greenberg, Shirley A McMahon and Michael A. Deem 105
Letter to Editor, Michael D. Stein 327
Sodium Chloride and Water Transport, see *Current Concepts*
Some Order from Chaos (Letter to Editor), Eugene E. Bleck 77

Special Articles:

Review of Mandatory Continuing Medical Education in Oregon, Merle Pennington 80
Letters to Editor, Mary Riggs, Roger C. Smith .. 249
Makings of Policy for Medicine and Health—A Report on the Institute of Medicine, John R. Hogness 88
Traumatic Injury—A Health Care Crisis, Donald D. Trunkey, Robert C. Lim, Jr., and F. William Blaisdell 92
Editorial 71
Letter to Editor, Thomas K. Hunt 250
A New Ethic for Medicine?, Albert R. Jonsen 169
Editorial 156
Medical Investigation of Alleged Rape, The, Irving Root, Wendell Ogden and Wayne Scott .. 329
Caveats for PSRO's, Kerr L. White 338
Editorial 314
Medicine and Public Health in the People's Republic of China—Observations and Reflections of a Recent Visitor, Philip R. Lee 430

Specialty Conferences:

Potpourri of Adenoviral Infections (UC, San Diego, and University Hospital of San Diego County, Pediatric Grand Rounds), Participants: James D. Connor, Richard M. Buchta, Frank DeGenaro, Jr., Mary Ann Fletcher, and William L. Nyhan .. 55
Editorial, Henry R. Shinefield 67
Idiopathic Acute Symmetrical Polyradiculoneuritis —The Landry-Guillain-Barré Syndrome (UC, San Diego, and University Hospital of San Diego County Pediatric Grand Rounds), Participants: Roger N. Rosenberg and Guillermo Mendoza ... 124
Editorial, Arthur K. Asbury 153
Thromboembolism—Diagnosis and Treatment (Stanford University), Moderator: Stanley L. Schrier; Chief Discussant: Arthur J. Silvergleid 219
Editorial, Samuel I. Rapaport 239
Letter to Editor, Jorge Franco, et al 419
Ventricular Septal Defect in Infancy (UC, San Diego, and University Hospital of San Diego County), Participants: William F. Friedman and Paul T. Pitlick 295
Editorial, Julien I. E. Hoffman 315
Viral Infections of the Fetus (UC, Los Angeles, and Harbor General Hospital Teaching Conference), Moderator: David T. Imagawa; Participants: Milan Fiala, Joseph W. St. Geme, Jr., Terry Yamauchi, and David T. Imagawa 369
Editorial, Eli Gold 407
Male Transsexualism (UC, San Diego, and San Diego Veterans Administration Hospital, Psychiatric Grand Rounds), Participants: Robert Gerner, Lewis Judd, Arnold Mandell, Stephen Millman, Zane Parzen and Robert Stoller 376
Editorial Comment, Norman M. Fisk 386
Gonococcal Infections—Laboratory, Clinical and Epidemiological Aspects (UC, Los Angeles, and Harbor General Hospital Teaching Conference), Moderator: Bascom F. Anthony 456

Laboratory Diagnosis of Neisseria Gonorrhoeae, Robert N. Yoshimori 456
Extra-Genital Manifestations of Gonococcal Disease, James S. Louie 458
Pediatric Aspects of Gonococcal Disease, Bascom F. Anthony 458
Epidemiology and Management of Gonorrhea, Thomas F. Keys 459
Editorial, David J. Drutz 485

Stanford University, see *Specialty Conferences*

Statements and Position Papers:

Access to Medical Care as a Citizen's Right (Committee on Role of Medicine in Society and House of Delegates) 438
Practical Criteria for the Diagnosis of Alcoholism in Hospital Practice (Committee on Alcoholism and Other Drug Dependence, Scientific Board, and House of Delegates) 438

Sterilization, see *Birth Control*
Sternal-Costal Infection with Pseudomonas—A Complication of Drug Abuse, Thomas F. Keys 72
Suppressed Plasma Renin Activity and Primary Aldosteronism (American Heart Association Clinical Cardiology), Paul I. Jagger 348
Surgical Aspects of Disc Lesion Management, see *Conservative and*
Syphilis (Medical Staff Conference) 46

T

Tachycardia, see *Cardiac Arrest*
Technetium 99M, see *Skeletal Scintigraphy*
Thermography in Venous Thrombosis (Letter to Editor), Jorge A. Franco, Bernadine Kovaleski, Klitia Vanags, Monika Schrier 419
Thrombosis, see *Venous*
Thromboembolism—Diagnosis and Treatment (Stanford University Specialty Conference), Chief Discussant: Arthur J. Silvergleid 219
Editorial, Samuel I. Rapaport 239
Letter to Editor, Jorge Franco, Bernadine Kovaleski, Klitia Vanags, Monika Schrier 419
Thyroid Crisis, see *Hyperthyroidism*
Trauma, see *Hepatic Artery Injury*

Trauma Rounds:

Penetrating Abdominal Wounds, Chief Discussant: Lynn F. Baker 252
Editorial 240
Role of Hyperalimentation in Patients with Multiple Injuries, The, Chief Discussant: George F. Sheldon 334
Management of Pelvic Fractures, Chief Discussant: Michael Chapman 421
Indications for Laparotomy Following Blunt Abdominal Injury, Chief Discussant: F. William Blaisdell 502

Traumatic Injury—A Health Care Crisis (Special Article), Donald D. Trunkey, Robert C. Lim, Jr., and F. William Blaisdell 92
Editorial 71
Letter to Editor, Thomas K. Hunt 250
Transsexualism, see *Male*
Treatment of a Cutaneous Nocardia Asteroides Infection with Minocycline Hydrochloride, Ervin Epstein 497
Treatment of Ventricular Septal Defect (Editorial), Julien I. E. Hoffman 315
Tricuspid Valve Replacement in Carcinoid Heart Disease, Harold G. Lund, Richard J. Cleveland, Lowell H. Greenberg, Maurice Lippmann and Malin R. Dollinger 412
Tumors of the Uterus, see *Mixed Mesodermal*

U

Ubiquitous Adenovirus, The (Editorial), Henry R. Shinefield 67
UC, Los Angeles, see *Specialty Conferences*
UC, San Diego, see *Psychiatric Rounds*
UC, San Diego, see *Specialty Conferences*
Unconscious Patient, The (Editorial), Fred Plum . 152
University Hospital of San Diego County, see *Specialty Conferences*
University of Oregon Medical School (Medical Schools of the West), Thelma Wilson 255
Uterus, see *Mixed Mesodermal Tumors*

V

Valve Replacement, see *Tricuspid*
Varicella, see *Acute Cerebellar Ataxia of Children*
[Venereal Disease], see *Gonococcal Infections*
[Venereal Disease], see *Syphilis*
Venous Thrombosis, see *Thermography*
Venous Thrombosis—Newer Diagnostic and Therapeutic Approaches (Editorial), Samuel I. Rapaport 239
Ventricular Septal Defect, see *Treatment of*
Ventricular Septal Defect in Infancy (UC, San Diego, and University Hospital of San Diego County), Participants: William F. Friedman and Paul T. Pitlick 295
Editorial, Julien I. E. Hoffman 315
Verminous Ophthalmia (Letter to Editor), Karl J. Chiapella 500
Vibrio Fetus, see *Human Infection with*
Viral Infections of the Fetus (UC, Los Angeles, and Harbor General Hospital Teaching Hospital), Moderator: David T. Imagawa; Participants: Milan Fiala, Joseph W. St. Geme, Jr., Terry Yamauchi, and David T. Imagawa (Specialty Conference) 369
Editorial, Eli Gold 407
Voice for Medicine in the West (Editorial) 67
von Willebrand's Disease, see *Hemophilia and*

W

Water Hemlock, see *Poison Hemlock*
Wolff-Parkinson-White Syndrome, see *Cardiac Arrest*
Women Physicians, see *Attitudes Toward*

Y

Young Adults, see *Family Planning Services for*

Integument!

Our skin—the human integument—covers us, defines us, protects us. But skin is subject to cuts, burns, abrasions. And infections. Neosporin Ointment fights infection by providing broad antibacterial action against susceptible skin invaders. It contains antibiotics that are rarely used systemically, reducing the risk of sensitization.

INDICATIONS: *Therapeutically*, used as an adjunct to appropriate systemic therapy for topical infections, primary or secondary, due to susceptible organisms, as in: • infected burns, skin grafts, surgical incisions, otitis externa • primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis) • traumatic lesions, inflamed or suppurating as a result of bacterial infection.

Prophylactically, the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing.

CONTRAINDICATIONS: Not for use in the external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of the components.

PRECAUTION: As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms and/or fungi. Appropriate measures should be taken if this occurs. Articles in the current medical literature indicate an increase in the prevalence of persons allergic to neomycin. The possibility of such a reaction should be borne in mind.

Complete literature available on request from Professional Services Dept. PML.

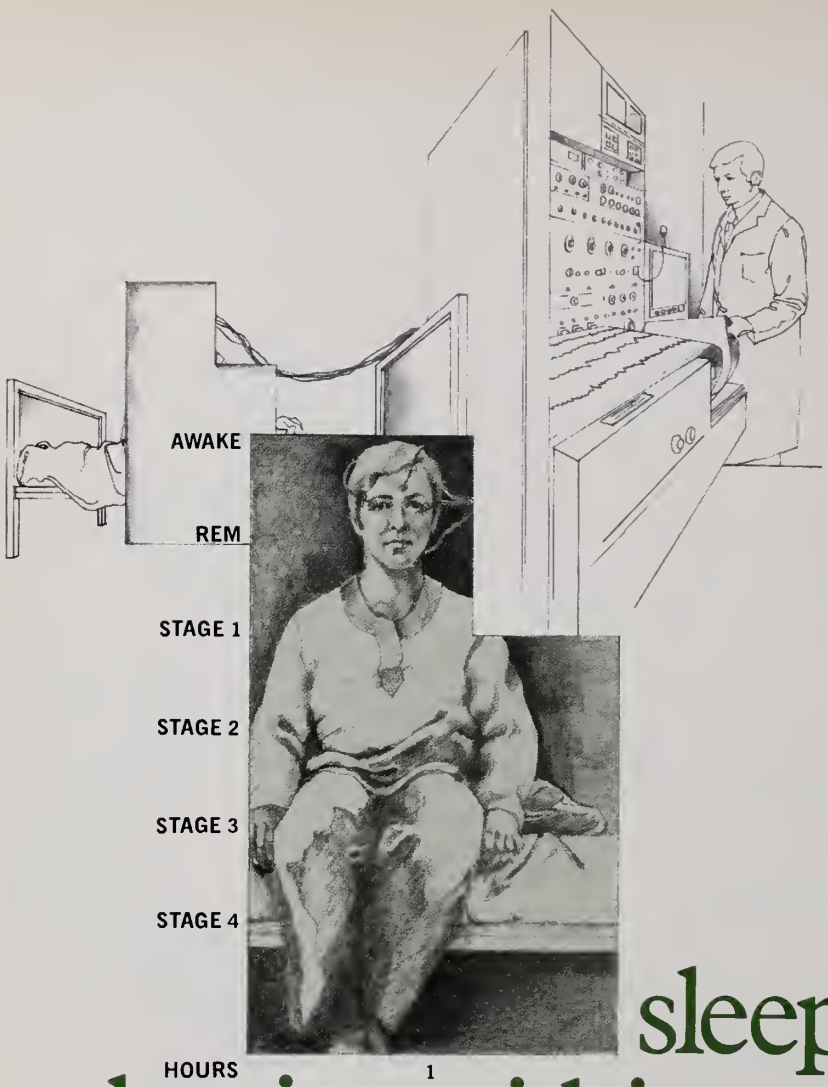
NEOSPORIN® Ointment

(POLYMYXIN B-BACITRACIN-NEOMYCIN)

Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5,000 units; zinc bacitracin 400 units; neomycin sulfate 5 mg. (equivalent to 3.5 mg. neomycin base); special white petrolatum q.s. In tubes of 1 oz. and ½ oz. and 1/32 oz. (approx.) foil packets.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709



sleep begins within 17 minutes, on average...

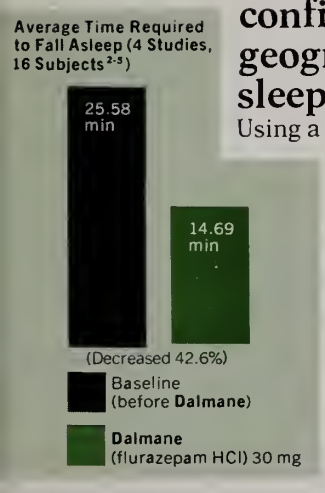
an initial benefit of

Dalmane®

(flurazepam HCl)

proved by a 22-night clinical study of insomnia patients in the sleep research laboratory and at home[1]

Three insomnia patients selected for difficulty falling asleep were administered Dalmane (flurazepam HCl) 30 mg for 14 consecutive nights. Placebo was given for four nights prior to and four nights after Dalmane. Physiologic tracings on Dalmane nights 1-3 showed sleep induction time averaged 13.90 minutes; on Dalmane nights 12-14, 18.80 minutes. Combined average for the 6 monitored drug nights was 16.35 minutes.[1]



confirmed by clinical studies in four geographically separated sleep research laboratories[2-5]

Using a 14-night protocol involving eight insomniac and eight normal subjects, four studies confirmed the sleep-inducing effectiveness of Dalmane (flurazepam HCl) and the reproducibility of this response. On average, one 30-mg capsule induced sleep within 17 minutes. In all these studies, Dalmane induced sleep rapidly, reduced nighttime awakenings, and provided 7 to 8 hours of sleep without repeating dosage.[2-5]

Dalmane (flurazepam HCl) induces and maintains sleep, with relative safety

Dalmane is generally well tolerated; morning "hang-over" has been relatively infrequent. While dizziness, drowsiness, lightheadedness and the like have been noted most often, particularly in the elderly and debilitated, physicians should be aware of the possibility of more serious reactions, as noted below.

Before prescribing Dalmane (flurazepam HCl), please consult Complete Product Information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; and in acute or chronic medical situations requiring restful sleep. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

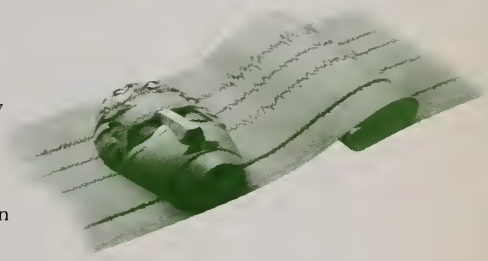
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, (e.g., excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.



when restful sleep is indicated

Dalmane®
(flurazepam HCl)

One 30-mg capsule *h.s.* — usual adult dosage (15 mg may suffice in some patients).
One 15-mg capsule *h.s.* — initial dosage for elderly or debilitated patients.

- **induces sleep within 17 minutes, on average**
- **reduces nighttime awakenings**
- **sustains sleep 7 to 8 hours, on average, without repeating dosage**

REFERENCES: 1. Kales A, *et al*: *Arch Gen Psychiatry 23*:226-232, Sep 1970
Karacan I, Williams RL, Smith JR: The sleep laboratory in the investigation of sleep and sleep disturbances. Scientific exhibit at the 124th annual meeting of the American Psychiatric Association, Washington DC, May 3-7, 1971
Frost JD Jr: Data on file, Medical Department, Hoffmann-La Roche Inc, Nutley NJ
Vogel GW: Data on file, Medical Department, Hoffmann-La Roche Inc, Nutley NJ
Dement WC: Data on file, Medical Department, Hoffmann-La Roche Inc, Nutley NJ

ROCHE

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

second wind for bronchospastics

QUIBRON PLUS®

Each capsule or tablespoon (15 ml.) elixir contains: theophylline (anhydrous) 150 mg., glyceryl guaiacolate 100 mg., ephedrine HCl 25 mg., and butabarbital 20 mg. *(Warning:* may be habit-forming). Elixir: alcohol 15%

the balanced bronchodilator

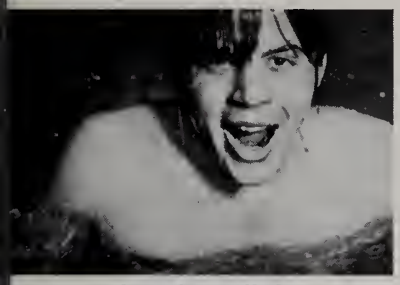
- Quibron Plus provides a balance of bronchodilation, sedation, and expectorant activity in a unique formulation
- theophylline PLUS ephedrine for relief of bronchiolar constriction
- PLUS glyceryl guaiacolate to facilitate expectoration
- PLUS butabarbital, the mild, intermediate-acting sedative

Mead Johnson LABORATORIES

For brief summary, please see facing page.

QUIBRON PLUS®

ch capsule or tablespoon (15 ml.) elixir contains: eophylline (anhydrous) 150 mg., glyceryl guaiate 100 mg., ephedrine HCl 25 mg., and butabartal 20 mg. *(Warning: may be habit-forming).* Elixir: cohol 15%



r comprehensive relief many bronchospastic disorders

Indications: Based on a review of a similar drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: bronchial asthma; bronchitis, bronchiectasis, and emphysema in which bronchospasm is present; the relief of bronchospasm; hay fever; nasal allergy; or for use as an expectorant.
Final classification of the less-than-effective indications requires further investigation.

Dosage: Adults: 1-2 capsules or 1-2 tablespoons elixir 2-3 times daily. Children 8 to 12: 1 capsule or 1 tablespoon elixir (15 ml.) 2-3 times daily. Children under 8: Up to ½ teaspoon (2.5 ml.) elixir per 10 lb. body weight, 2-3 times daily. Dosage should be adjusted on an individual basis.
Contraindications: Contraindicated in patients who are sensitive to any ingredient of the formulation.
Precautions: Do not administer more frequently than every 6 hours, or within 1 hours after rectal dose of any preparation containing theophylline or aminophylline. Do not give other compounds containing xanthine derivatives concurrently. Use cautiously in patients with cardiovascular disease, hypertension, hyperthyroidism, prostatic hypertrophy, hepatic disease, impaired renal function, glaucoma, diabetes. Do not exceed recommended dose. Be aware of the possible effects from concomitant doses of other sympathomimetic amines. Caution parents against overdosage in children.
Adverse Reactions: Theophylline may exert some stimulating effect on the central nervous system. Its administration may cause local irritation of the gastric mucosa, with possible gastric discomfort, nausea, and vomiting. Taking Quibron Plus after meals may help avoid such disturbances. *Central Nervous System:* Nervousness, jitteriness, vertigo, and sedation; *Cardiovascular:* Tachycardia (palpitation); *Miscellaneous:* Precordial pain.
How Supplied: Elixir in bottles of 1 pint; capsules in bottles of 100.

Mead Johnson
LABORATORIES
©1973 MEAD JOHNSON & COMPANY
EVANSVILLE, INDIANA 47721 U.S.A. 734022

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

THE ART OF LEARNING MEDICINE—May H. Lesser. Appleton-Century-Crofts, Division of Prentice-Hall, Inc., New York City (Prentice-Hall, Inc., Englewood Cliffs, NJ 07632), 1974. 343 pages, with 303 illustrations, sketches, in black and white and color, price not quoted.

ARTHRITIS—Sheldon Paul Blau, MD; and Dodi Schultz. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1974. 176 pages, $5.95.

BRONCHIAL ASTHMA—Current Immunologic, Pathophysiologic and Management Concepts—Nicholas J. Gross, MD, PhD, Department of Medicine, University of Chicago, Pritzker School of Medicine. Medical Department, Harper & Row, Publishers, Inc., 2350 Virginia Ave., Hagerstown, MD (21740), 1974. 88 pages, $3.95 (Paperback).

CARDIOVASCULAR DISEASES—Guidelines for Prevention and Care—Reports of the Inter-Society Commission for Heart Disease Resources—Edited by Irving S. Wright, MD, National Chairman; and Donald T. Fredrickson, MD, Project Director, Inter-Society Commission for Heart Disease Resources, New York City. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402, Stock Number 1727-0035. 404 pages, $6.95.

DUNCAN'S DISEASES OF METABOLISM—Seventh Edition—Two Volumes—Vol. I: Genetics and Metabolism—Vol. II: Endocrinology—Edited by Philip K. Bondy, MD, C.N.H. Long Professor of Medicine, Yale University; and Leon E. Rosenberg, MD, Professor and Chairman, Department of Human Genetics; Professor of Pediatrics and Medicine, Yale University. W. B. Saunders Company, West Washington Square, Philadelphia (19105), 1974. 948 pages, Vol. I, 736 pages, Vol. II $52.00 (both volumes), $26.00 (one volume).

A HANDBOOK OF HUMAN SERVICE ORGANIZATIONS—Edited by Harold W. Demone, Jr., PhD, Executive Vice President, United Community Services of Metropolitan Boston, and Associate Clinical Professor of Social Welfare, Harvard Medical School; and Dwight Harshbarger, PhD, Organizational consultant for the West Virginia Department of Mental Health, Associate Professor of Psychology, West Virginia University. Behavioral Publications, 72 Fifth Avenue, New York City (10011), 1974. 624 pages, $19.95; 5 or more Student Editions, $15.95.

GOLD & SILVER coins

BUY FOR CASH!

IMMEDIATE DELIVERY

SILVER DOLLARS
SILVER COINS IN BAGS

(213) 278-0674 CALL OR WRITE (714) 548-7796

LIBERTY COIN COMPANY
9465 Wilshire Blvd., Suite 428
Beverly Hills, CA 90212
RUSH DETAILS TO:

Name_____
Address_____
City_____ Zip_____
Phone No._____

Classified Advertisements

The rate for each insertion is **$2.50 per line** (average six words per line) **with five line minimum.**

Box number charge: $1.50 each month.

Classified display rates $25.00 per inch.

Copy for classified advertisements should be received not later than **the fifth of the month preceding issue.** • Classified advertisers using Box Numbers forbid the disclosure of their identity. Your inquiries in writing will be forwarded to Box Number advertisers. The right is reserved to reject or modify all classified advertising copy in conformity with the rules of the Advertising Committee.

CLASSIFIED ADVERTISEMENTS ARE PAYABLE IN ADVANCE

PHYSICIANS WANTED

RESIDENCIES & INTERNSHIPS—BAKERSFIELD, KERN COUNTY: Accepting applications for 1975-76. First year residencies in fully approved four year clinically oriented program (non pyramid). Applicants requiring one or more years of General Surgery for sub-specialty welcome. Full patient responsibility, supervision by full-time Board Certified General and Thoracic Chairman and Associate Director, with full-time Board Certified Neurosurgeon, Urologist and Anesthesiologist. Board Certified attending staff in plastic and ortho surgery. Salary $13,080 annually; meals. Must be eligible for California license. Contact: Chairman, Department of Surgery, Kern General Hospital, 1830 Flower Street, 93305. Phone (805) 323-7651, ext. 214.

FAMILY PRACTICE DOCTOR to join two doctor family practice group — four-day week, four weeks vacation plus two weeks for postgraduate studies. Suburban area near Rose Bowl-California. Prefer board or board eligible family practitioner. $3.250 per month to start and partnership after one year. Near three major hospitals. Both doctors teaching S.C. and Loma Linda Medical Schools; (213) 790-1103.

INTERNIST, GENERALIST AND UROLOGIST, State Veterans Home and Hospital. Salary depending upon training, experience and position to be filled. Excellent retirement plan and other benefits. Located one hour from San Francisco in beautiful Napa Valley. Call or write John P. Preston, Administrator, Phone (707) 944-2422.

PROGRESSIVE RURAL GROUP PRACTICE—Located in the Salinas Valley near MONTEREY and CARMEL has an immediate need for two Family Practitioners and an Internist (Generalist) to join an established 9-man group practice, plus 11 consultants, incorporated in 1970. Competitive starting salary and top fringe benefits. Brochure by return mail. Please call or send C.V. to: DUANE F. HYDE, MD, Southern Monterey County Medical Group (A Professional Corporation), 210 Canal St., King City, CA 93930, Tel. (408) 385-5471.

WANTED FOR COMPREHENSIVE SIX-MAN expanding medical care corporation—Family Practitioner and Internist. Small, friendly city with big-city advantages; two colleges, close to Los Angeles, San Francisco, Las Vegas, ocean, mountains. All sports, four-day week, every seventh week-end on call. Good salary first year. Permanent corporation membership after first year. Write to M. E. Baurer, MD, Manor Medical Group, Inc., 223 China Grade Loop, Bakersfield, CA 93308.

PEDIATRICIAN:—Board Certified or eligible. Primary clinical and academic opportunity. Full-time position, 332-bed county/community hospital with UCLA association. Approved internship, residencies in Internal Medicine, Surgery, Ob-Gyn, General Practice, Pathology, and Ophthalmology. California license required. Salary Civil Service $34,692, or contract negotiable. Send curriculum vitae (or call 805-323-7651) Robert W. Huntington, Jr., MD, 1830 Flower Street, Bakersfield, CA 93305.

PHYSICIANS WANTED

PSYCHIATRISTS AND GENERAL PHYSICIANS—Immediate employment in modern mental hospital fifty miles north of Los Angeles. Pleasant surroundings. Salaries from $23,484 to $31,488. Contact Robert E. Moebius, MD, Chief of Professional Education, Camarillo State Hospital, Box A, Camarillo, CA 93010. (805) 482-4671, extension 2893.

PSYCHIATRISTS, GP'S for geriatric program within State hospital 50 miles north of Los Angeles. Fine climate near beaches. Salary $23,484 to $31,488. Optional monthly OD 5% extra. Other fringe benefits. Contact: Martin Gish, MD, Program Director (6G), Box A, Camarillo, CA 93010. Telephone (805) 482-4671, ext. 2638.

PULMONARY MEDICINE—Internist wanted to join cardio-pulmonary group In Southern California. Finest smog-free coastal community. Excellent place to live and practice. Live within walking distance of office and hospital. Write P.O. Box 3197, Ventura, CA 93003.

SANTA BARBARA, CALIFORNIA. Ideal coastal community. Expanding medical staff at County-operated teaching hospital has openings for full-time physicians in Family Practice, Ob-Gyn, and Anesthesiology. Competitive salary and fringe benefits. Contact: Edgar Rosen, MD, Medical Director, Santa Barbara General Hospital, 300 San Antonio Road, P.O. Box 3650, Santa Barbara, CA 93105. Phone (805) 967-2311.

IT'S LATER THAN YOU THINK!—Tired of the same routine? Want a life style change? Join an expanding Group Practice HMO in Southern California Beach Communities. More than 10 years in HMO practice. Limited number of openings, all specialties. Inquire today. Frank Volpe, MD, Family Health Program, Room 6419, 2925 N. Palo Verde, Long Beach, CA 90815.

PROTECT YOUR FUTURE—Join an established growing Group practice. Career opportunity $32,000 to $36,000 per year to start with regular increases, plus tax free benefits and generous pension program. Frank Volpe, MD, Medical Director, Family Health Program, Room 6419, 2925 N. Palo Verde, Long Beach, CA 90815.

ISLAND LIVING with all conveniences, plus one week each two months to visit Japan, Hong Kong, Manila, Taipei and other islands. Career opportunity to return to mainland to an established Group Practice HMO on a permanent basis. More than 10 years in HMO practice. Family Health Program Catholic Medical Center, Tamuning, Guam. Write to Delbert Stokesbary, MD, Family Health Program, Room 6419, 2925 N. Palo Verde, Long Beach, CA 90815.

GENERAL SURGEON and **THORACIC-VASCULAR SURGEON;** Board Certified or Board Eligible. 200-bed GM&S Hospital in San Francisco Bay Area. Salary to $36,000 depending on qualifications, supplemented by attractive benefits; retirement, life and health insurance, liberal leave system; opportunity for medical school affilliation; provisions for paid continuing education programs. An equal opportunity employer. Contact Chief, Surgical Service, Veterans Administration Hospital, Livermore, CA 94550. 415-447-2560.

COLLEGE HEALTH SERVICE PHYSICIAN—To start Sept. 1, 1974. Work 10 months out of the year. Interested in person competent in handling gynecological service and rendering general medical service to college-age clientele. Part time position with possibility of full time. Write inquiry to Director, Student Health Service, California State College, Sonoma, 1801 E. Cotati Ave., Rohnert Park, CA 94928. We are an affirmative action employer.

CANTONESE-SPEAKING PHYSICIAN, preferably internist or family practitioner for comprehensive health center, $23,061 to $32,448. C.V. to North East Medical Services, 615 Grant, San Francisco, CA 94108.

ANESTHESIOLOGIST wanted, Board Certified or eligible. To join a 4-man group in 187 bed hospital. Full accreditation. San Francisco East Bay area. Gross of $5-6 thousand monthly can be expected. Wide range of surgery, including thoracic and neurosurgery. Obstetrical anesthesia planned. Write to Dean Van Metre, Administrator, St. Rose Hospital, 27200 Calaroga Ave., Hayward, CA 94545.

PHYSICIANS WANTED

PUBLIC HEALTH PHYSICIAN—Number two position in a progressive county health department having 73 employees. Will assist in planning, organizing and conducting county-wide public health program and will be responsible for specific program elements and clinics. Salary in range of $26,460 to $32,160 per year. Very pleasant working environment, generous employee benefits, five day-40 hour week, and semi-rural, centrally located community in which to live. Must be California licensed MD or license eligible. No residency or public health experience required. Contact: C. O. SHEPHEARD, Stanislaus County Personnel Office, Room 305, Courthouse, 1100 Eye St., Modesto, CA 95354 or phone collect: (209) 526-6341.

PUBLIC HEALTH DIRECTOR—Riverside, California. Outstanding opportunity with dynamic, expanding, Southern California County Health Department. Program responsibility includes both public and mental health services. The perfect residential and recreational location, Riverside County offers an ideal climate, abundant natural scenic beauty, and is just an hour's drive from mountain, desert, and beach resort areas. Requires eligibility for certification in Preventive Medicine, Internal Medicine, or Pediatrics, and 5 years public health experience including 2 years in an administrative capacity. Filing deadline—July 1. For further information contact Sue Morgan, Riverside County Personnel Department, 4080 Lemon St., Room 11, Riverside, CA 92501.

ASSISTANT RESEARCH SURGEONS, SURGICAL ONCOLOGY—The Division of Oncology, Department of Surgery, UCLA School of Medicine, has positions for Assistant Research Surgeons in Surgical Oncology (2 years of surgical residency required) and positions as Assistant Professor of Surgery. Experience in cancer surgery, tumor immunology and chemotherapy preferred. Salary negotiable. An affirmative action employer. Applications from women and minority groups encouraged. Please direct inquiries to Donald L. Morton, MD, Chief, Division of Oncology, Department of Surgery, UCLA School of Medicine, Los Angeles, CA 90024.

SITUATIONS WANTED

GENERAL SURGEON, age 58, wants to relocate in Southern California. Willing to do ER work, general practice and general surgery. Author of textbook and 100 publications. Write Box 9378, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

BOARD CERTIFIED RADIOLOGIST, well experienced in diagnosis, including angiography and isotopes. now on staff of large well known private hospital, as well as on clinical faculty of University, wishes to relocate. Interested In hospital or group practice, WILLING TO INVEST. Box 9382, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

OPHTHALMOLOGIST 30, energetic, hard-working, married, completing University of Pennsylvania residency, seeks partnership, associate, or group practice in Northern or Southern California. Available fall '74. Write Box 9388, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103, or call (609) 784-6751.

SACRAMENTO, CALIFORNIA

FOUNDATION-SPONSORED PRIMARY CARE GROUP

Excellent opportunity for four Board-eligible FAMILY PRACTITIONERS in new modern facilities in the heart of rapidly growing community. Great hospital access. Positions available beginning May 1, 1974. Annual minimum salary of $20,000 guaranteed from fee-for-service practice. Position includes eligibility for appointment to University of California-Davis School of Medicine teaching staff. Positions too attractive to delay. Send confidential curriculum vitae to:

CHARLES B. FRENCH, MD
Project Director

MEDICAL CARE FOUNDATION OF SACRAMENTO
650 Howe Avenue
Sacramento, California, 95825

INDUSTRIAL PHYSICIAN

Full or Part Time

Duties include providing pre-employment, executive, and special physicals and handling first aid and medical emergencies.

We would be very much interested in a physician/surgeon who would like to retire from general practice yet continue to practice medicine in a pleasant, well-equipped medical facility.

The opening is for either a full or part time physician. The hours and days are negotiable, although our needs are greatest on Mondays and during the morning hours. We have a 40-hour week and an exceptional benefit plan which includes income insurance and a savings plan.

Requirements: MD degree, California license, U.S. citizenship, and several years of experience.

Please call
MR. CAREY BAKER
(213) 391-0711, Ext. 2494
Hughes Aircraft Company
Aerospace Divisions
Culver City, California

5th INTERNATIONAL CONGRESS OF SOCIAL PSYCHIATRY ATHENS SEPT. 1-7, 1974

15-day independent tour from August 30-September 14 inclusive. Jet roundtrip LAX-NYC-Athens, accommodations in doubles with bath, superior class hotel, breakfasts, dinners, 7-day cruise on luxurious "TTS Atlas" with 3 meals daily, transfers, guides, social program for dependents.

FROM NYC FROM $804—FROM LOS ANGELES FROM $998

FOR RESERVATIONS, INFORMATION AND BROCHURE CONTACT:
American Student Travel Association
924 Westwood Boulevard, at UCLA
Los Angeles, CA 90024
Telephone (213) 479-4444

THE WESTERN Journal of Medicine

CLASSIFIED RATES

$2.50 PER LINE

(Average six words per line)

FIVE LINE MINIMUM

BOX NUMBERS $1.50 EXTRA

(Classified Advertising is payable in advance)

PRACTICES FOR SALE

SOUTHERN CALIFORNIA, ORANGE COUNTY—Solo Ped Practice available near University Teaching Hospital: Relocating to new Bldg June '74. Active and growing, over $100,000 gross last year. Good coverage for Nite and Vacations. Cash or terms available. Write Box 9387, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

GOING PRACTICE—12-year stand in heart of Palm Desert, Calif. with 8 rooms of equipment; (714) 346-1111.

ALLERGY PRACTICE—Gross $120,000 on 3-day schedule—opportunity to expand. Retiring doctor—desirable suburb of Los Angeles. Box No. 9389, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ASSOCIATE WANTED

OPTOMETRIST with well-established practice in Laguna Hills-El Toro area (Orange County) wants **OPHTHALMOLOGIST** associate. Write Box 9386, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

HOUSE TO RENT

SPACIOUS LAKE TAHOE HOUSE for rent July, August, three bedrooms, three baths, plus loft. G. Tolbert, P.O. Box 963, Tahoe City, CA 95730; (916) 583-4445.

OFFICES FOR LEASE OR RENT

BERKELEY, CALIFORNIA—Good opportunity for Internist to establish private practice, or Family Practitioner, at Dwightmil Medical Center, 2505 Milvia St., adjacent to Herrick Hospital. Phone (415) 845-2391.

FULLY EQUIPPED MEDICAL OFFICE—Ready for immediate occupancy, in a fast growing community of Fairfield, California. Please call (707) 425-6216.

ORANGE COUNTY, Coastal City. Medical office for sub-lease; full decorated and plumbed. Ideal for pediatrics, ENT, general practice, obstetrics, surgery. Centrally located. 4 hospitals within 10 minutes. Population 150,000 projected 280,000 within 10 years. Box 9385, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103, or call (714) 962-6671

MEDIUM SUITE, three treatment rooms, four dentists in building—181 E. 18th St., Costa Mesa, CA 92627; Phone (714) 548-1262.

SAN JOSE MEDICAL ARTS PLAZA—Ultra modern Medical-Dental Suites designed to specific requirements of medical specialty. Building contains Radiology and Pathology Laboratories, Physical Therapy, Pharmacy, Answering Service and Central Billing. Abundant covered and open parking. Desirable location adjacent to hospital and freeway interchange. NOW LEASING. 2444 Moorpark Ave., San Jose, CA 95128; (408) 288-6650.

MEDICAL OFFICE FOR RENT—Well furnished, x-ray, copier, refrigerator. Was used 19 years by semi-retired family physician. Interested in competent replacement, good opportunity. Between Point Reyes and San Rafael. Two general practitioners in San Anselmo, Fairfax and adjacent area involves 12,000 or more people. Rent, equipment open to discussion; (415) 453-2757.

TEXTBOOKS FOR SALE

MANUAL OF ROUTINE ORDERS FOR MEDICAL AND SURGICAL EMERGENCIES
published by
WARREN GREEN, Inc.
10 South Brentwood Boulevard
St. Louis, Missouri 63105

MEDICAL DIRECTOR
Micronesia

New Health Maintenance Organization has been established on Guam, U.S.A. Backed by more than ten years of mainland HMO experience. New facilities with all major specialties, dentistry and pharmacy and with extensive lab and x-ray.

This is your opportunity to learn prepaid group practice—the wave of the future.

Tropical Island living with all conveniences plus one week each two months for excursion rate visits to Japan, Hong Kong, Australia. Career opportunity either to remain or return to our Southern California HMO on a permanent basis.

Send résumé to
FRANK VOLPE, MD, Medical Director, Family Health Program, Room 6419, 2925 Palo Verde Ave., Long Beach, CA 90815.

COMPTON FOUNDATION HOSPITAL

820 West Compton Boulevard
COMPTON, CALIFORNIA 90220
(213) 537-3070
(213) 631-1148

G. CRESWELL BURNS, M.D.
Administrator and Medical Director

HELEN RISLOW BURNS, M.D.
Assistant Medical Director

MEMBER OF
American Hospital Association
and
National Association of Private Psychiatric Hospitals

High Standards of Psychiatric Treatment . . . Serving the Los Angeles Area

Accredited by Joint Commission on Accreditation of Hospitals

IN GONORRHEA

INJECTION

Wycillin®

(STERILE PROCAINE PENICILLIN G SUSPENSION) WYETH

Gonorrhea, according to the national Center for Disease Control, is, if the parenteral route is chosen, most effectively treated with aqueous procaine penicillin G. In uncomplicated cases, administration of 4.8 million units together with 1 gram oral probenecid, given at least 30 minutes prior to injection, is recommended.

Indications: In treatment of moderately severe infections due to penicillin G-sensitive microorganisms sensitive to the low and persistent serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

NOTE: When high sustained serum levels are required use aqueous penicillin G, IM or IV.

The following infection will usually respond to adequate dosages of intramuscular procaine penicillin G.—*N. gonorrhoeae:* acute and chronic (without bacteremia).

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy.

Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen and intravenous corticosteroids should also be administered as indicated.

Although anaphylaxis is more frequent following parenteral therapy it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injections may produce neurovascular damage.

A small percentage of patients are sensitive to procaine. If there is a history of sensitivity, make the usual test: Inject intradermally 0.1 cc. of a 1 to 2 percent procaine solution. Development of an erythema, wheal, flare or eruption indicates procaine sensitivity. Sensitivity should be treated by the usual methods, including barbiturates, and procaine penicillin preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reaction.

The use of antibiotics may result in overgrowth of nonsusceptible organisms. Constant observation of the patient is essential. If new infections due to bacteria or fungi appear during therapy, discontinue penicillin and take appropriate measures.

If allergic reaction occurs, withdraw penicillin unless, in the opinion of the physician, the condition being treated is life threatening and amenable only to penicillin therapy.

When treating gonococcal infections with suspected primary or secondary syphilis, perform proper diagnostic procedures, including darkfield examinations. In all cases in which concomitant syphilis is suspected, perform monthly serological tests for at least four months.

Adverse Reactions: (Penicillin has significant index of sensitization) skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum sickness-like reactions, including chills, fever, edema, arthralgia and prostration. Severe and often fatal anaphylaxis has been reported.(See "Warnings.")

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Administer only by *deep intramuscular injection,* in upper outer quadrant of buttock. In infants and small children, midlateral aspect of thigh may be preferable. When doses are repeated, vary injection site. Before injection, aspirate to be sure needle bevel is not in blood vessel. If blood appears, remove needle and inject in another site.

Although some isolates of *Neisseria gonorrhoeae* have decreased susceptibility to penicillin, this resistance is relative, not absolute, and penicillin in large doses remains the drug of choice. Physicians are cautioned not to use less than recommended doses.

Gonorrheal infections (uncomplicated)—Men or Women: 4.8 million units intramuscularly divided into at least two doses and injected at different sites at one visit, together with 1 gram of oral probenecid, preferably given at least 30 minutes prior to injection.

NOTE: Treatment of severe complications of gonorrhea should be individualized using large amounts of short-acting penicillin. Gonorrheal endocarditis should be treated intensively with aqueous penicillin G. Prophylactic or epidemiologic treatment for gonorrhea (male and female) is accomplished with same treatment schedules as for uncomplicated gonorrhea.

Retreatment: The National Center for Disease Control, Venereal Disease Branch, U.S. Dept. H.E.W. recommends:

Test cure procedures at approximately 7-14 days after therapy. In the male, a gram-stained smear is adequate if positive; otherwise, a culture specimen should be obtained from the anterior urethra. In the female, culture specimens should be obtained from both the endocervical and anal canal sites.

Retreatment in males is indicated if urethral discharge persists 3 or more days following initial therapy and smear or culture remains positive. Follow-up treatment consists of 4.8 million units, I.M. divided in 2 injection sites at single visit.

In uncomplicated gonorrhea in the female, retreatment is indicated if follow-up cervical or rectal cultures remain positive for *N. gonorrhoeae.* Follow-up treatment consists of 4.8 million units daily on 2 successive days.

Syphilis: all gonorrhea patients should have a serologic test for syphilis at the time of diagnosis. Patients with gonorrhea who also have syphilis should be given additional treatment appropriate to the stage of syphilis.

Composition: Each TUBEX® disposable syringe 2,400,000 units (4-cc. size) contains procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer, and as w/v approximately 0.7% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. The multiple-dose 10-cc. vial contains per cc. 300,000 units procaine penicillin G in a stabilized aqueous suspension with sodium citrate buffer and approximately 7 mg. lecithin, 2 mg. carboxymethylcellulose, 3 mg. polyvinylpyrrolidone, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Five are graduating with honors. How many with VD?

On the average, you can figure the incidence of VD among teenagers at about 900 per 100,000 population.* And growing.

Among those in the 20-24 age-group, the incidence is even higher. And it, too, is growing.

In the long run, a populace educated to the risks and prevention of VD is probably the best answer to the problem. Meanwhile, though, adequate doses of the recommended types of penicillin remain a formidable weapon.

IN SYPHILIS
INJECTION
Bicillin® LONG-ACTING
(STERILE BENZATHINE PENICILLIN G SUSPENSION) WYETH

Syphilis is preferably treated with benzathine penicillin G, which is also the drug of choice for prophylaxis after exposure. Administration of 2.4 million units (1.2 million in each buttock) usually cures most cases of primary, secondary and latent syphilis with negative spinal fluid.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular benzathine penicillin G.—Venereal infections: Syphilis, yaws, bejel and pinta.

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens.

Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of nonsusceptible organisms including fungi. Take appropriate measures should superinfection occur.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high doses of parenteral penicillin.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Administration and Dosage: Venereal infections—

Syphilis—Primary, secondary and latent—2.4 million units (1 dose).

Late (tertiary and neurosyphilis)—2.4 million units at 7 day intervals for three doses.

Congenital—under 2 years of age, 50,000 units/Kg. body weight; ages 2-12 years, adjust dosage based on adult dosage schedule.

(Shake multiple-dose vial vigorously before withdrawing the desired dose.) Administer by **deep intramuscular injection** in the upper outer quadrant of the buttock. In infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site. Before injecting the dose, aspirate to be sure needle bevel is not in a blood vessel. If blood appears, remove the needle and inject in another site.

Composition: 2,400,000 units in 4-cc. single dose disposable syringe. Each TUBEX disposable syringe also contains in aqueous suspension with sodium citrate buffer, as w/v approximately 0.5% lecithin, 0.4% carboxymethylcellulose, 0.4% polyvinylpyrrolidone, 0.01% propylparaben and 0.09% methylparaben. Units benzathine penicillin G (as active ingredient); 300,000 units per cc.—10-cc. multi-dose vial. Each cc. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. polyvinylpyrrolidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 0.14 mg. propylparaben and 1.2 mg. methylparaben.

Wyeth Laboratories
Philadelphia, Pa. 19101

*U.S. Dept. of Health, Education, and Welfare: VD Fact Sheet 1972. Publication No. (HSM) 73-8195.

THE NATURAL WAY

For more than thirty years PREMARIN (Conjugated Estrogen Tablets, U.S.P.) has been prepared with natural equine estrogens exclusively—without synthetic estrogen supplements. For more than thirty years it has provided the complete estrogen complex in the proportions found in its natural source. And for more than thirty years PREMARIN has enjoyed an unparalleled record of clinical efficacy and acceptance.

PREMARIN. The only estrogen preparation available that contains natural estrogens exclusively and als meets all U.S.P. specifications for conjugated estrogens. Assurance of quality for you and your patients.

PREMARIN . . . naturally.

BRIEF SUMMARY
(For full prescribing information, see package circular.)
PREMARIN®
(Conjugated Estrogens Tablets, U.S.P.)

Indications: Based on a review of PREMARIN Tablets by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications for use as follows:
Effective: As replacement therapy for naturally occurring or surgically induced estrogen deficiency states associated with: the climacteric, including the menopausal syndrome and postmenopause; senile vaginitis and kraurosis vulvae, with or without pruritus.
"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

Contraindications: Short acting estrogens are contraindicated in patients with (1) markedly impaired liver function; (2) known or suspected carcinoma of the breast, except those cases of progressing disease not amenable to surgery or irradiation occurring in women who are at least 5 years postmenopausal; (3) known or suspected estrogen-dependent neoplasia, such as carcinoma of the endometrium; (4) thromboembolic disorders, thrombophlebitis, cerebral embolism, or in patients with a past history of these conditions; (5) undiagnosed abnormal genital bleeding.
Warnings: Estrogen therapy should not be given to women with recurrent chronic mastitis or abnormal mammograms except, if in the opinion of the physician, it is warranted despite the possibility of aggravation of the mastitis or stimulation of undiagnosed estrogen-dependent neoplasia.

The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, estrogen therapy should be discontinued immediately.

Estrogens may be excreted in the mother's milk and an estrogenic effect upon the infant has been described. The long range effect on the nursing infant cannot be determined at this time.

Hypercalcemia may occur in as many as 15 percent of breast cancer patients with metastases, and this usually indicates progression of bone metastases. This occurrence depends neither on dose nor on immobilization. In the presence of progression of the cancer or hypercalcemia, estrogen administration should be stopped.

A statistically significant association has been reported between maternal ingestion of diethylstilbestrol during pregnancy and the occurrence of vaginal carcinoma in the offspring. This occurred with the use of diethylstilbestrol for the treatment of threatened abortion or high risk pregnancies. Whether or not such an association is applicable to all estrogens is not known at this time. In view of this finding, however, the use of any estrogen in pregnancy is not recommended.

Failure to control abnormal uterine bleeding or unexpected recurrence is an indication for curettage.
Precautions: As with all short acting estrogens, the following precautions should be observed:

A complete pretreatment physical examination should be performed with special reference to pelvic and breast examinations.

To avoid prolonged stimulation of the endometrium and breasts in climacteric or hypogonadal women, estrogens should be administered cyclically (3 week regimen with 1 week rest period—withdrawal bleeding may occur during rest period).

Because of individual variation in endogenous estrogen production, relative overdosage may occur which could cause undesirable effects such as abnormal or excessive uterine bleeding, mastodynia and edema.

Because of salt and water retention associated with estrogenic anabolic activity, estrogens should be used with caution in patients with epilepsy, migraine, asthma, cardiac, or renal disease.

If unexplained or excessive vaginal bleeding should occur, reexamination should be made for organic pathology.

Pre-existing uterine fibromyomata may increase in size while using estrogens; therefore, patients should be examined at regular intervals while receiving estrogenic therapy.

The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

Because of their effects on epiphyseal closure, estrogens should be used judiciously in young patients in whom bone growth is incomplete.

Prolonged high dosages of estrogens will inhibit anterior pituitary functions. This should be borne in mind when treating patients in whom fertility is desired.

The age of the patient constitutes no absolute limiting factor, although treatment with estrogens may mask the onset of the climacteric.

Certain liver and endocrine function tests may be affected by exogenous estrogen administration. If test results are abnormal in a patient taking estrogen, they should be repeated after estrogen has been withdrawn for one cycle.
Adverse Reactions: The following adverse reactions have been reported associated with short acting estrogen administration:
nausea, vomiting, anorexia
gastrointestinal symptoms such as abdominal cramps and bloating
breakthrough bleeding, spotting, unusually heavy withdrawal bleeding (See DOSAGE AND ADMINISTRATION)
breast tenderness and enlargement
reactivation of endometriosis
possible diminution of lactation when given immediately postpartum
loss of libido and gynecomastia in males
edema
aggravation of migraine headaches
change in body weight (increase, decrease)
headache
allergic rash
hepatic cutaneous porphyria becoming manifest
Dosage and Administration: PREMARIN should be administered cyclically (3 weeks of daily estrogen and 1 week off) for all indications except selected cases of carcinoma and prevention of postpartum breast engorgement.

Menopausal Syndrome—1.25 mg. daily, cyclically. Adjust dosage upward or downward according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

If the patient has not menstruated within the last two months or more, cyclic administration is started arbitrarily. If the patient is menstruating, cyclic administration is started on day 5 of bleeding. If breakthrough bleeding (bleeding or spotting during estrogen therapy) occurs, increase estrogen dosage as needed to stop bleeding. In the following cycle, employ the dosage level used to stop breakthrough bleeding in the previous cycle. In subsequent cycles, the estrogen dosage is gradually reduced to the lowest level which will maintain the patient symptom-free.

Postmenopause—as a protective measure against estrogen deficiency-induced degenerative changes (*e.g.* osteoporosis, atrophic vaginitis, kraurosis vulvae)—0.3 mg. to 1.25 mg. daily and cyclically. Adjust dosage to lowest effective level.

Osteoporosis (to retard progression)—usual dosage 1.25 mg. daily and cyclically.

Senile Vaginitis, Kraurosis Vulvae with or without Pruritus—0.3 mg. to 1.25 mg. or more daily, depending upon the tissue response of the individual patient. Administer cyclically.
How Supplied: PREMARIN (Conjugated Estrogens Tablets, U.S.P.)

No. 865—Each *purple* tablet contains 2.5 mg., in bottles of 100 and 1,000.

No. 866—Each *yellow* tablet contains 1.25 mg., in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 867—Each *red* tablet contains 0.625 mg., in bottles of 100 and 1,000.

No. 868—Each *green* tablet contains 0.3 mg., in bottles of 100 and 1,000. 7352

PREMARIN®

BRAND OF CONJUGATED ESTROGENS TABLETS, U.S.P.

CONTAINS ONLY NATURAL ESTROGENS ...NO SYNTHETICS OR SUPPLEMENTS

Ayerst.

AYERST LABORATORIES
New York, N.Y. 10017

Bio-Science Reports

Serum Parathyroid Hormone as a Diagnostic Aid

An accurate measurement of the serum level of parathyroid hormone (PTH) with results reported from the laboratory within about ten days is now available. The diagnosis of diseases of the parathyroid has always been a difficult, serious problem and we now have a powerful laboratory tool which will help solve some of the diagnostic dilemmas and further stimulate research in this field.

The classic laboratory findings in primary hyperparathyroidism are, of course, high serum calcium and low serum phosphorus; high urinary calcium is also commonly found. Increased phosphate excretion due to inhibition of phosphate reabsorption (TRP) and measurement of the TRP are additional laboratory aids for diagnosing hyperparathyroidism. All of these tests are obviously indirect procedures for establishing the diagnosis so there is a distinct value in having a direct measure of PTH.

In spite of the complexity and difficulty of the radioimmunoassay technic for PTH, it is now possible to quantitate the hormone with reasonable precision and in most cases to differentiate normal from hyperparathyroid serum levels. Human PTH is not available in sufficient quantities to use as an antigen or standard, but guinea pig antiserum to bovine PTH has sufficient cross-reactivity with human PTH to allow its effective use in the assay.

Unfortunately, the lack of a human parathyroid standard complicates any comparison of results from different laboratories. At Bio-Science a purified bovine PTH preparation is used as the standard and results are expressed as equivalents of purified bovine PTH. The antiserum used gives similar curves with both human serum PTH and purified bovine PTH and does not distinguish between the two.

The specimen requirement for the PTH assay is: 5 ml. frozen serum obtained from blood which has been drawn between 6 and 9 a.m. while the patient is in the rested, fasting state. The blood should be drawn with a chilled syringe or Vacutainer and kept in an ice bath until the serum can be separated, preferably in a refrigerated centrifuge. Separation of the serum from the cells and freezing should be completed as soon as possible. The frozen serum should be sent to us packed in dry-ice. Shipping containers intended for frozen specimen shipments are available without charge.

Write or call, collect, for additional literature on this subject and containers for mailing.

25 YEARS

Main Lab: 7600 Tyrone Ave., Van Nuys, California 91405

Philadelphia Branch: 116 So. Eighteenth St., Philadelphia, Pa. 19103

Bio-Science Laboratories
7600 Tyrone Avenue
Van Nuys, California 91405 Dept. BB
or
116 So. Eighteenth St.
Philadelphia, Pa. 19103

Gentlemen: Please send me, without obligation:

- ☐ A copy of your Handbook of Specialized Diagnostic Laboratory Tests
- ☐ A lab pack containing a small supply of postage-paid mailing containers and Fee Schedule
- ☐ Information on _____ (write in name of test)

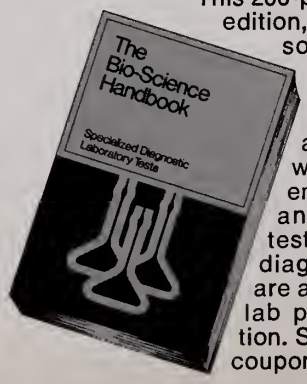
Name _____

Address _____

City _____ State _____ Zip _____

FREE

HANDBOOK OF SPECIALIZED DIAGNOSTIC LABORATORY TESTS



This 200-page book, now in its tenth edition, is a uniquely informative source to keep you up-to-date on the newer laboratory tests, such as parathyroid hormone, available to clinicians. You will find it a handy reference guide for normal values and quick summations on tests which can aid in your diagnostic problems. Copies are available to physicians and lab personnel without obligation. Simply fill out and mail this coupon.

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington, Montana, Alaska, Idaho

CALIFORNIA and HAWAII

COMMITTEE ON CONTINUING MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in **California and Hawaii** is supplied by the Committee on Continuing Medical Education of the California Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000. Note: Please see **California Medicine**, Vol. 117, No. 4, October, 1972 issue for a list of organizations approved for Category I Credit toward the CMA Certificate in Continuing Medical Education.

ALCOHOLISM AND DRUG USE

June 24-28—**Institute on Drug Dependency.** LLU. Monday-Friday. $75. Contact: Center for Dependent Behavior, LLU School of Health, Loma Linda 92354.

CANCER

July 22-25—**Cancer of the Skin and Mouth—Advances in Diagnosis and Treatment.** STAN. Monday-Thursday. 28 hrs. $200.

September 7-8—**Early Diagnosis of Breast Cancer.** UCLA. Saturday-Sunday.

Continuously—**Tumor Conference.** UCSD at Pickard Auditorium, University Hospital, San Diego. Tuesdays, 4:00 p.m. Contact: Sidney Saltzstein, MD, University Hospital, San Diego. (714) 291-3330, ext. 1071.

Continuously — **Tumor Board — Harbor General Hospital.** Pathology Conference Room, Harbor General Hospital, Torrance. Fridays 3-4 p.m. Advice and consultation from specialists (UCLA faculty members) in surgical, medical, and radiotherapeutic treatment of cancer. Practicing physicians invited to have patients presented for discussion. Contact: John R. Benfield, MD, Dept. of Surgery, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 281.

MEDICINE

June 14—**Advances in Internal Medicine.** UCSF. Friday.

June 18-July 30—**Advances in Hematology.** UCD Extension at St. Joseph's Hospital, Stockton. Tuesdays, 7:30-9:30 p.m. $40. Contact: Rene Mack, University Extension, UCD, Davis 95616.

June 21-23—**Coronary Disease/Exercise Testing/Rehabilitation Therapy.** International Medical Corp. at Fairmont Hotel, San Francisco. Friday-Sunday. $175. Contact: William E. James, Ph.D., Dir. of Professional Education, International Medical Corp., 2865 S. Colorado Blvd., Denver, Colo. 80222. (303) 757-7875.

July 27—**New Concepts in Respiratory Therapy Management.** UCD. Saturday.

September 13—**Course in Armchair Allergy.** PMC. Friday.

September 19-21—**The Relevance of Animal Models to Human Dermato-Pharmacology and Dermato-Toxicology.** UCSF. Thursday-Saturday. 11 hrs. $200.

October 2-5—**Present Concepts in Internal Medicine.** Letterman Army Medical Center, San Francisco. Wednesday-Saturday. 24 hrs. Contact: John J. Deller, C, Dept. of Medicine, Letterman Army Med. Ctr., Presidio, San Francisco 94129. (415) 561-4275.

October 7-11—**Common Problems in Primary Care.** See Of Interest to All, October 7-11.

October 8—**Paul M. Aggeler Visiting Professor—5th Annual.** UCSF at San Francisco General Hospital. Tuesday, 11:00 a.m-12:00 noon. Judith G. Pool, Ph.D., Stanford, will talk on her research on hemophilia during a year's sabbatical at Oxford Univ. Contact: Susan Nutter, S.F. Gen. Hosp., San Francisco. (415) 648-8200, ext. 404.

October 17-20—**California Society of Internal Medicine—Annual Meeting.** Ahwahnee Hotel, Yosemite. Thursday-Sunday. 8 hrs. Contact: Carol H. Handley, Exec. Dir., CSIM, 1412 Central Towers, 703 Market St., San Francisco 94103. (415) 362-1548.

October 18—**Recent Advances in Rheumatology.** UCD at Woodlake Inn, Sacramento. Friday.

October 18-19—**San Diego County Heart Association.** Sheraton-Harbor Island Hotel, San Diego. Friday-Saturday. Con-

(Continued on Page 39)

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

LLU: Loma Linda University
Contact: John E. Peterson, MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311.

PMC: Pacific Medical Center
Contact: Allen J. Enelow, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 321-1200, ext. 5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92664. (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Donald Brayton, MD, Director Continuing Education in Medicine and the Health Sciences. P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Richard A. Lockwood, MD, Associate Dean for Health Manpower, 1310 Basic Sciences Building, University of California, San Diego, School of Medicine, La Jolla 92037. (714) 453-2000, ext. 1251.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-2342.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 225-1511, ext. 203.

When low back pain* interferes...

Help relieve pain, restore mobility with

PARAFON FORTE® Tablets

PARAFLEX® (chlorzoxazone)† 250 mg.; TYLENOL® (acetaminophen) 300 mg

*This drug has been evaluated as "possibly" effective for this indication.

See brief summary of prescribing information on facing page for Indications, Contraindications, Warnings, Precautions and Adverse Reactions.

© McN 73

PARAFON FORTE® Tablets help relieve pain, restore mobility and stop pain-spasm feedback by providing:

a non salicylate analgesic equal to aspirin for relief of pain,[1,2] yet unlikely to cause the gastric irritation,[2,3] allergic reactions[2] or increased bleeding time[4] associated with aspirin therapy.

and a skeletal muscle relaxant shown in extensive clinical studies to be useful in a variety of low back disorders[5-7]* but which is not an antihistamine or tranquilizer derivative and is unlikely to produce a tranquilizing or sedative effect.[8]

***Indications** Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective for the relief of severe skeletal muscle pain and spasm when associated with acute disorders of the lower back (including acute exacerbations of chronic conditions).

Contraindications: Sensitivity to either component.
Warnings: *Usage in Pregnancy*—Use in woman of child-bearing potential only when potential benefits outweigh possible risks.
Precautions: Exercise caution in patients with known allergies or history of drug allergies. If a sensitivity reaction or any signs or symptoms suggestive of liver dysfunction are observed, the drug should be stopped.
Adverse Reactions: Occasionally, drowsiness, dizziness, lightheadedness, malaise, overstimulation or gastrointestinal disturbances may be noted; rarely, allergic-type skin rashes, petechiae, ecchymoses, angioneurotic edema or anaphylactic reactions. In rare instances, *Paraflex* (chlorzoxazone) may possibly have been associated with gastrointestinal bleeding. While *Paraflex* (chlorzoxazone) and chlorzoxazone-containing products have been suspected as being the cause of hepatic toxicity in approximately eighteen patients, it was not possible to state that the dysfunction was or was not drug induced
Usual Adult Dosage: Two tablets q.i.d
Supplied: Scored, light green tablets, imprinted "McNEIL"—bottles of 100.

References: **1.** Batterman, R.C., and Grossman, A.J. Fed. Proc. *14* 316, 1955. **2.** Goodman, L.S., and Gilman, A., ed. The Pharmacological Basis of Therapeutics, ed. 4. New York, The Macmillan Company, 1970. **3.** Vickers, F.N. Gastroint. Endosc. *14*:94, 1967. **4.** Mielke, C.H., Jr., and Britten, A.F.H.: New Engl. J. Med. *282* 1270, 1970 (Corresp.). **5.** Vernon, W.G. Curr. Therap. Res. *14* 801, 1972. **6.** Scheiner, J.J. Curr. Therap. Res. *14* 168, 1972. **7.** Walker, J.M. Curr. Therap. Res. *15* 248, 1973. **8.** Friend, D.G. Clin. Pharmacol. Ther. *5* 871, 1964

†U.S. Patent No. 2,895,877

McNEIL McNeil Laboratories, Inc. Fort Washington, Pa. 19034

(Continued from Page 37)

tact: Mrs. Cathy Ware, Prog. Dir., SDCHA, 3640 Fifth Ave., P.O. Box 3625, San Diego 92103. (714) 291-7454.

October 24-26—**West Coast Allergy Society—13th Annual Scientific Program.** St. Francis Hotel, San Francisco. Thursday-Saturday. 19 hrs. $25 for members; $30 non-members. Contact: Daniel K. Billmeyer, MD, Prog. Chr., 2164 S.W. Park Pl., Portland 97205. (503) 226-1555.

October 25-26—**Clinical Gastroenterology.** Scripps Clinic and Research Foundation, La Jolla. Friday-Saturday. Contact: Williamson B. Strum, MD, Div. of Gastroenterology, Scripps Clinic & Research Foundation, 476 Prospect St., La Jolla 92037.

Continuously—**Recertification Review Course—Internal Medicine.** USC at Louis B. Mayer Medical Teaching Center, Keith Admin. Bldg. Tuesdays and Thursdays, 7-10 p.m. April 9-October 10, 1974. Sessions will cover 9 broad topics of internal medicine; each topic will have 5 evening sessions.

Continuously—**Clinical Conferences.** Community Hospital of Santa Cruz. See Of Interest to All, Continuously.

Continuously—**Medical Chest Conference.** St. Mary's Hospital, San Francisco. Tuesdays, 4:00-5:00 p.m. in Pulmonary Classroom. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Medical Morbidity-Mortality Conference.** St. Mary's Hospital, San Francisco. Thursdays, 12:15-1:00 p.m. in Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Cardiology Conferences.** San Diego County Heart Association at Sharp Hospital, San Diego. Fridays, 8-10 a.m. Contact: William Kuzman, MD, Sharp Hospital, 7901 Frost St., San Diego. (714) 277-6121. Or Mrs. Cathy Ware, SDCHA, P.O. Box 3625, San Diego 92103. (714) 291-7454.

Continuously—**Clinical Cardiology Conferences.** San Diego County Heart Association at University Hospital, San Diego. Thursdays, 8-10 p.m. Contact: Robert O'Rourke, MD, Instructor, Univ. Hospital, San Diego. (714) 294-5663. Or Mrs. Cathy Ware, Prog. Dir., San Diego Co. Heart Assn., 3640 5th St., San Diego 92103. (714) 291-7454.

Continuously—**Renal Dialysis Traineeships.** UCSF. By special arrangement.

Continuously—**Preceptorships in Biochemistry and Biophysics.** UCSF. By arrangement.

Continuously—**Clinics in Dermatology.** UCSF. By arrangement.

Continuously—**Cardiovascular Seminars.** Mondays at 4:30 p.m. in the second floor lecture hall, Basic Science Building, UCSD. Contact: UCSD.

Continuously—**Preceptorships in Cardiology.** PMC. By arrangement. $200 per mo.; $500 for 3 mos. Contact: Arthur Selzer, MD, PMC.

Continuously—**Preceptorships in Practical Office Dermatology.** PMC. Wednesdays or Fridays, 9:00 a.m.-12:00 noon, for 10 weeks. Periods begin Oct., Jan., or April. $100. Contact: Harold M. Schneidman, MD, Dept. of Dermatology, PMC.

Continuously—**Preceptorships in Infectious Disease.** PMC. Full time for four weeks. To be arranged. $250. Contact: Rodney J. Valentine, MD, Chief, Div. of Infectious Diseases, PMC.

Continuously—**Biomedical Lecture Series.** UCSD. Specified Wednesday at 8:00 p.m. For schedule contact UCSD.

Continuously—**Joint Continuing Medical Education Programs for South Bay Hospitals.** UCSD, Bay General Hospital, Chula Vista Community Hospital, Coronado Hospital, Paradise Valley Hospital and CRMP. Programs to be held at various hospitals. Contact: UCSD.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: 1975—date and place to be announced.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: Los Angeles Convention Center, Los Angeles, February 22-26, 1975.

Hawaii Medical Association—510 S. Beretania St., Honolulu 96813. Annual Meeting—Ilikai Hotel, Honolulu, October 29-November 1, 1974.

Idaho Medical Association—407 W. Bannock St., Boise 83702. Annual Meeting: Lodge, Sun Valley, July 24-27, 1974.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: Big Sky of Montana, Big Sky, September 12-14, 1974.

Nevada State Medical Association—3660 Baker Lane, Reno 89501. Annual Meeting: Stockmen's, Elko, September 27-29, 1974.

Oregon Medical Association—2164 SW Park Pl., Portland 97205. Annual Meeting: Hilton Hotel, Portland, September 11-15, 1974.

Washington State Medical Association—444 NE Ravenna Blvd., #108, Seattle 98115. Annual Meeting: Davenport Hotel, Spokane, September 22-25, 1974.

Continuously—**Renal Conference.** San Joaquin General Hospital, Stockton. First Thursday of each month, 11:00 a.m. to 12:00 noon, Conference Room 2. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Wednesday of each month, 10:00-11:30 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Seminar in Clinical and Public Health Aspects of Chest Diseases.** Harbor General Hospital and CRMP Area IV at Harbor General Hospital, Torrance. Three-hour sessions on second Friday of every other month, 9-12 a.m., B-3 classroom, Chest Wards. Presentation of patients demonstrating medical, social, and public health aspects of chest disease, followed by discussion of cases. Course open to physicians, nurses, social workers and personnel concerned with detection and management of patients with chest disease. No fee. Contact: Matthew Locks, MD, Dir., Chest Ward Service, Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1245.

Continuously—**Training of Physicians in Modern Concepts of Pulmonary Care.** CRMP Area VI, LLU and Riverside General Hospital. Four weeks or more, scheduled by arrangement. Diagnostic and therapeutic methods in medical chest disease, physiological methodology of modern pulmonary care programs, use of new instrumentation in the field. 160 hrs. Contact: George C. Burton, MD, LLU.

Continuously—**Continuing Education in Internal Medicine—Harbor General Hospital.** CRMP Area IV and Harbor General Hospital at Harbor General Hospital, Torrance. Thursdays 12:00-1:00 p.m. Systematic review of internal medicine, lectures by faculty and visiting professors. Contact: A. James Lewis, MD, Program Dir., Harbor General Hospital, 1000 W. Carson St., Torrance 90509. (213) 328-2380, ext. 1534.

Continuously—**Training for Physicians in General Internal Medicine.** LLU. Four weeks or more, scheduled by arrangement. Bedside and classroom training, practical aspects of clinical care and management. 160 hrs. Contact: LLU.

Continuously—**Cardiology Conferences — CRMP Area III.** Monthly, 2:30-5:30 p.m. at Room M112, Stanford Medical Center, Stanford. Conferences including case presentations of local complicated cardiological problems. Contact: William J. Fowkes, Jr., MD, 703 Welch Road, Suite G1, Palo Alto 94304. (415) 321-1200, ext. 6015.

Grand Rounds—Medicine

Tuesdays

8:30-10:00 a.m., Assembly Hall, Harbor General Hospital, Torrance. UCLA.

9:00-10:00 a.m., Morrissey Hall, St. Mary's Hospital, San Francisco.

Neurologist in Chief Rounds. 12:30 p.m., 6 East, University Hospital of San Diego County, San Diego. UCSD.

Wednesdays

8:00 a.m., A Level Amphitheater, LLU Hospital, LLU.

8:30 a.m., Auditorium, Brown Bldg., Mt. Sinai Hospital, Los Angeles. UCLA.

1st Wednesday of each month, 10:00-11:15 a.m., Conference Room 1, San Joaquin General Hospital, Stockton.

10:30-12 noon. Auditorium, Medical Sciences Building. UCSF.

11:00 a.m., Room 1645, Los Angeles County-USC Medical Center. USC.

12:00 noon. Auditorium, School of Nursing, Orange County Medical Center. UCI.

12:30-1:30 p.m., University Hospital, UCSD.

12:30-1:30 p.m., Building 22, VA Hospital, Sepulveda.

Thursdays

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

8:00-10:00 a.m., 4th Floor, UCLA Medical Center. UCLA.

Neurology. 11:00 a.m., 664 Science, UCSF.

Neurology. 12:30 p.m., University Hospital of San Diego County, San Diego. UCSD.

4th Thursday of each month, 12:30 p.m. in lower conference room, Huntington Intercommunity Hospital, Huntington Beach.

Fridays

8:00 a.m., Auditorium, First Floor, Kern County General Hospital, Bakersfield. UCLA.

8:30-10:00 a.m., Auditorium, Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles. UCLA. Second and Fourth Fridays.

Neurology. 8:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Clinicopathologic Conference. 1st Friday, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

Internal Medicine. 2nd, 3rd, and 4th Fridays, 12:00-1:30 p.m., Staff Room, St. Mary's Long Beach Hospital, Long Beach.

1:15 p.m., Lieb Amphitheater, Timken-Sturgis Research Bldg., La Jolla. Scripps Clinic and Research Foundation.

Rheumatology. 11:45 a.m., Room 6441, Los Angeles County-USC Medical Center, Los Angeles. USC.

MENTAL RETARDATION

September 29-October 11—**Mental Retardation.** UCLA. 13 days.

OBSTETRICS AND GYNECOLOGY

October 14-15—**New Horizons in Perinatal Intensive Care.** Harbor General Hospital at Marriott Hotel, Los Angeles. Monday-Tuesday. 13 hrs. $125. Contact: Bonnie Stapleton, Cont. Ed. Coord., Harbor Gen. Hosp., 1124 W. Carson, Torrance 90502. (213) 775-7711, ext. 1373.

October 20-23—**International Family Planning Research Association.** Gene Autry Hotel, Palm Springs. Sunday-Wednesday. Contact: Ludwig Lauerhass, Exec. Dir., 2960 W. 8th St., Los Angeles 90005. (213) 386-1970.

Continuously—**Ob/Gyn Conference.** San Joaquin General Hospital, Stockton. Mondays, 12:00-1:30 p.m. in Doctors' Dining Room. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. See Radiology and Pathology, Continuously.

Grand Rounds—Obstetrics and Gynecology

Mondays

10:30 a.m., Assembly Room, First Floor, Harbor General Hospital, Torrance. UCLA.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Wednesdays

8:00 a.m., Conference Room, Sacramento Medical Center, Sacramento. UCD.

8:00-9:00 a.m., Fourth Floor Auditorium, UCLA Medical Center. UCLA.

Fridays

8:00 a.m., Auditorium, Orange County Medical Center. UCI.

10:30 a.m., Auditorium, Women's Hospital, Los Angeles County-USC Medical Center, Los Angeles. USC.

Saturdays

8:00 a.m., Executive Dining Room, University Hospital of San Diego County, San Diego. UCSD.

PEDIATRICS

June 16-20—**1974 Birth Defects Conference.** Attending Staff Association, Harbor General Hospital at Newporter Inn, Newport Beach. Sunday-Thursday. Contact: David Rimoin, MD, Harbor Gen. Hosp., 1000 W. Carson, Torrance 90509. (213) 328-2380, ext. 1441.

June 21—**13th Annual Conference on Prematurity.** STAN. Friday.

September 11-12—**Brennemann Memorial Lectures—31st Annual.** Los Angeles Pediatric Society at Sportsmen's Lodge, North Hollywood. Wednesday-Thursday. Contact: Mrs. Eva Black, Exec. Sec., P.O. Box 2022, Inglewood 90305. (213) 757-1198.

September 13-14—**Endocrinology in the Pubescent and Adolescent.** Children's Hospital Medical Center, Oakland, at Highlands Inn, Carmel. Friday-Saturday. 8 hrs. $50. Contact: Inetta Carty Calori, Children's Hosp. Med. Ctr., 51st & Grove Sts., Oakland 94609. (415) 654-5600.

October 7-11—**Common Problems in Primary Care.** See Of Interest to All, October 7-11.

October 14-15—**New Horizons in Perinatal Intensive Care.** See Obstetrics and Gynecology, October 14-15.

October 19-23—**American Academy of Pediatrics.** Hilton Hotel, San Francisco. Saturday-Wednesday. Contact: Robert G. Frazier, MD, Exec. Dir., 1801 Hinman Ave., Evanston, Ill. 60204.

Continuously—**Perinatal Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 12:30 p.m., Conference Room. Contact: Marguerite Markarian, MD, Dir. of Nurseries, Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3261.

Continuously—**Pediatric Clinical Conference.** Earl and Loraine Miller Children's Hospital, Long Beach. Fridays, 8:00 a.m., Conference Room "H." Contact: Harry W. Orme, MD, Med. Dir., Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3228.

Continuously—**Preceptorships in Pediatrics.** UCSF. By arrangement.

Continuously—**Pediatric Cardiology Conference.** UCSD, Third Floor Conference Room, University Hospital. Clinical review of cases planned for the week, Tuesdays at 7:30 a.m.; Clinical review of data obtained, Fridays at 1:30 p.m. Contact: UCSD.

Continuously—**Pediatric Research Seminar.** UCSD. Mondays, 12 noon-1:00 p.m.

Continuously—**Pediatrics Clinical Conference.** San Joaquin General Hospital, Stockton. Wednesdays, 10:00-11:15 a.m., and Fridays, 9:30-11:00 a.m., Conference Room 3. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric-Cardiology Conference.** San Joaquin General Hospital, Stockton. Third Thursday of each month, 9:30-11:00 a.m., Conference Room 2. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Pediatric Cardiology Conference.** St. Vincent's Hospital, Los Angeles. Fourth Thursday of each month, 2:00 p.m., Main Doheny Conference Room. Contact: Leonard M. Linde, MD, Chief, Pediatric Cardiology, St. Vincent's Hospital, 3rd and Alvarado Sts., Los Angeles.

Continuously — **Pediatric Conference.** Cedars-Sinai Medical Center, Los Angeles. Thursdays weekly, 8:30-9:30 a.m. Contact: B. M. Kagan, MD, Lebanon Hall, Cedars-Sinai Med. Center, 4833 Fountain Ave., Los Angeles 90029. (213) 662-9111, ext. 181.

Grand Rounds—Pediatrics

Tuesdays

8:00 a.m., Children's Hospital Medical Center, Oakland.

8:30 a.m., Pathology Auditorium, San Francisco General Hospital.

8:30 a.m., University Hospital of San Diego County, San Diego. UCSD.

11:30 a.m., Auditorium, Pediatric Pavilion, Los Angeles County-USC Medical Center, Los Angeles. USC.

12:00 noon, A Level Amphitheater, LLU Hospital, LLU.

Wednesdays

8-9:00 a.m., held alternately at Auditorium, Orange County Medical Center and Auditorium, Children's Hospital of Orange County. UCI.

8:30 a.m., Bothin Auditorium, Children's Hospital, San Francisco.

Thursdays

8:30 a.m., First Floor Auditorium, Harbor General Hospital, Torrance.

8:30-10:00 a.m., Room 664, Science Building, UCSF.

8:30-9:30 a.m., Lebanon Hall, Cedars of Lebanon Hospital, Los Angeles.

Fridays

8:30 a.m., Lecture Room, A Floor, Health Sciences Center, UCLA.

8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Pediatric Cardiology. 1st Friday of each month. 8:00 a.m., 5th floor Ward, St. Vincent's Hospital, Los Angeles.

8-9:00 a.m., Lecture Hall, Children's Hospital of Los Angeles.

8:30 a.m., Room M104, Stanford University Medical Center, STAN.

8:30-9:30 a.m., alternately at St. Mary's, Children's, Mt. Zion, and Kaiser Hospitals, San Francisco.

9:30-11:00 a.m., Conference Room 2, San Joaquin General Hospital, Stockton.

Infectious Disease. 10:00 a.m., Auditorium, Children's Division Building, Los Angeles County-USC Medical Center, Los Angeles. USC.

PSYCHIATRY

June 22-23—**Biofeedback: Theory and Clinical Applications.** UCD Extension at Stockton State Hospital, Stockton. Saturday-Sunday. Contact: Rene Mack, University Extension, UCD, Davis 95616.

June 24-28—**Comparative Psychotherapies.** USC Continuing Education in Psychiatry at Hilton Inn, San Diego. Monday-Friday. 20 hrs. $100. Contact: Donald H. Naftulin, MD, Dir., Cont. Ed. in Psych., USC. (213) 225-1511, ext. 336.

July 3-7—**Sexual Dysfunction.** UCLA at Residential Conference Center, Lake Arrowhead. Wednesday-Sunday.

July 7-10—**Biofeedback for Physicians.** UCLA at Lake Arrowhead. Sunday-Wednesday.

October 24-27—**American Academy of Child Psychiatry.** Fairmont Hotel, San Francisco. Thursday-Sunday. Contact: American Academy of Child Psychiatry, 1800 R Street, NW, Washington, D.C. 20009.

Continuously—**Adolescent Case Review.** St. Mary's Hospital, San Francisco. Wednesdays, 1:00-2:00 p.m., 3 West Conference Room. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Preceptorships in Psychiatry.** UCSF. By arrangement.

Grand Rounds—Psychiatry

Wednesdays

10:30 a.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

11:00 a.m., McAuley Institute, St. Mary's Hospital, San Francisco.

RADIOLOGY AND PATHOLOGY

July 13—**Dermal Pathology Slide Seminar.** Memorial Hospital Medical Center-UCI Center for Health Education at Memorial Hosp. Med. Ctr., Long Beach. Saturday. $80. Contact: Mrs. Margaret Frederick, Exec. Sec., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

September 22-23—**Society for Pediatric Radiology.** Hilton Hotel, San Francisco. Sunday-Monday. Contact: John P. Dorst, MD, Johns Hopkins Hospital, Baltimore, Md. 21205.

September 24-27—**American Roentgen Ray Society.** Hilton Hotel, San Francisco. Tuesday-Friday. Contact: Ted F. Leigh, MD, Emory University Clinic, Atlanta, Ga. 30322.

October 25-26—**Society of Nuclear Medicine, Northern & Southern California Chapters—Annual Meeting.** Hilton Hotel, San Francisco. Friday-Saturday. Contact: Society of Nuclear Medicine, No. Calif. Chapter, 1595 Soquel Dr., Santa Cruz. (408) 476-7300.

Continuously—**Ob/Gyn Correlated Pathology Conference.** St. Mary's Hospital, San Francisco. Mondays, 12:00 noon, Staff Lounge. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Pathology Conference.** St. Mary's Hospital, San Francisco. 2nd and 4th Wednesdays. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Tumor Board.** St. Mary's Hospital, San Francisco. Mondays, 8:00-9:00 a.m., Clinic Building, Room 3. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Clinical Pathology Conference.** St. Mary's Hospital, San Francisco. Third Tuesday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Radiology Film Reading Sessions.** Orange County Radiology Society and Orange County Medical Center at Orange County Medical Center, Orange. 1st Tuesday of each month, September-June, 7:30-9:00 p.m. Contact: Edward I. Miller, MD, 301 Newport Blvd., Newport Beach. (714) 645-8600.

Continuously—**Cytopathology Seminars.** UCSF. 2nd Thursday of each month, September-June. 5:00-6:00 p.m. Contact: Eileen King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously — **Cytopathology Tutorial Program.** UCSF. Courses may be arranged throughout the year on the basis of individual needs and goals; fees are prorated accordingly. Arrangements should be discussed with instructor, Eileen B. King, MD, Dept. of Pathology, UCSF. (415) 666-2919.

Continuously—**Principles and Clinical Uses of Radioisotopes.** UCSF. Fundamentals for the proper understanding and use of radioactivity in clinical medicine. Training in diagnostic and therapeutic uses of radioisotopes. Normal period of training: 3 months. Two-part course: Part A, Basic Fundamentals; Part B, Clinical Applications.

Continuously—**Scintillation Camera Workshop.** UCSF. Workshops provided for physicians and nuclear medicine technologists by special arrangement, limited to 30 trainees per workshop. One- or two-day intensive training periods, basic instruction in scintillation camera theory, scintographic principles and scintiphotographic interpretations. $50. Contact: UCSF.

Continuously — **Scintiphotograph Interpretation.** UCSF and Nuclear Medicine Section, Department of Radiology, UCSF. By special arrangement, designed to furnish physicians with an opportunity to participate in the daily activities of a university laboratory. Two-week training period participation in daily interpretation conferences, correlation conferences, routine training conferences. $175. Contact: UCSF.

Grand Rounds—Radiology-Pathology

Mondays

Pathology. 1:00 p.m., Sacramento Medical Center, Sacramento. UCD.

Tuesdays

Radiology. 3rd Tuesday of each month, 8:00 a.m., Bothin Auditorium, Children's Hospital and Adult Medical Center, San Francisco.

SURGERY AND ANESTHESIOLOGY

June 15—**Orthopaedic Surgery and Surgical Anatomy of the Neck and Upper Extremity.** International College of Surgeons, So. Calif. Division, at L.A. Orthopaedic Hospital, Los Angeles. Saturday. 8 hrs. $50. Contact: Darline Murphy, Exec. Sec., 136 N. Brighton, Burbank 91506. (213) 486-0669.

June 15-16—**Techniques in Respiratory Therapy.** American Society of Anesthesiologists at St. Francis Hotel, San Francisco. Saturday-Sunday. 13 hrs. $75 for members; $100, nonmembers. Contact: ASA, 515 Busse Highway, Park Ridge, Ill. 60068. (312) 825-5586.

June 22—**Ophthalmology Clinical Conference.** STAN. Saturday.

June 27-28—**Highlights of Modern Ophthalmology.** PMC. Thursday-Friday. 16 hrs.

June 27-29—**Phaco-Emulsification.** St. John's Hospital and So. Calif. Lions Eye Institute at St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

July 1-Sept. 13—**Basic Science Course in Ophthalmology,** STAN. 6 wks.

July 11-13—**Laser Photocoagulation and Fluorescein Angiography.** Palo Alto Medical Clinic, Palo Alto. Thursday-Saturday. 20 hrs. $300. Contact: H. Christian Zweng, MD, Palo Alto Medical Clinic, 300 Homer Ave., Palo Alto 94301. (415) 321-4121.

July 25-27—**Phaco-Emulsification.** St. John's Hospital and Southern California Lions Eye Institute at St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

August 3—**New Surgical Techniques in Strabismus.** Harbor General Hospital, Torrance. Saturday. 5 hrs. $35. Contact: Mrs. Bonnie Stapleton, Cont. Ed. Coord., Harbor Gen. Hosp., 1124 W. Carson St., Torrance 90502. (213) 775-7711, ext. 1373.

August 14-18—**Urology.** UCLA. Wednesday-Sunday.

September 26-28—**Phaco-Emulsification.** St. John's Hospital and Southern Calif. Lions Eye Institute at St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

September 26-28—**Cerebral Palsy—New Perspectives.** American Academy for Cerebral Palsy at Children's Hospital at Stanford. Thursday-Saturday. $75. Contact: E. E. Bleck, MD, Children's Hospital at Stanford, 520 Willow Rd., Palo Alto 94304.

September 26-28—**The Neck.** American Academy of Orthopaedic Surgeons. Anaheim. Thursday-Saturday. $150 for physicians; $50 residents. Contact: E. Shannon Stauffer, MD, Rancho Los Amigos Hospital, Downey 90242.

October 5-12—**Western Orthopedic Association.** Hawaii. One week. Contact: Ms. H. Jacqueline Martin, Exec. Sec., WOA, 354 21st St., Oakland 94612.

October 17-19—**Phaco-Emulsification.** St. John's Hospital and Southern Calif. Lions Eye Institute at St. John's Hospital, Santa Monica. Thursday-Saturday. Contact: Robert M. Sinskey, MD, 2222 Santa Monica Blvd., Santa Monica 90404.

October 31-November 1—**Strabismus.** PMC at Fairmont Hotel, San Francisco. Thursday-Friday.

Continuously—**Neurological Sciences.** St. Francis Hospital, Lynwood. Wednesdays, 7:30-8:30 a.m. Presentations of radiological evaluations and pathological specimens of current material and review of current topics in specialty. Weekly notification of cases available. Contact: Ralph Miller, Admin. Asst., St. Francis Hospital, 3630 Imperial Highway, Lynwood 90262. (213) 639-5111, ext. 365.

Continuously—**Basic Science Lecture Series.** Dept. of Surgery, St. Mary's Hospital, San Francisco. Mondays, 11:15 a.m.-12:15 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Medical Education, St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Mini Residencies in Orthopaedics.** STAN. Postgraduate traineeships of 4-14 days duration, as you wish. No tuition but donations accepted. Contact: Orthopaedic Division, Dept. of Surgery, Stanford.

Continuously—**Orthopedic Lecture Series.** Alternately at St. Mary's, St. Joseph's, Mary's Help, VA Martinez, Kaiser San Francisco, and Harkness Memorial Hospitals. Third Tuesday of each month, 6:00 p.m. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Orthopedic Trauma Conference.** USC at Los Angeles County-USC Medical Center. Mondays, 7:00-9:00 p.m. Contact: Dept. of Orthopedics, USC School of Med., 2025 Zonal Ave., Los Angeles 90033. (213) 225-3131.

Continuously—**Preceptorships in General Surgery.** UCSF. By arrangement.

Continuously—**Preceptorships in Neurological Surgery.** UCSF. By arrangement.

Continuously—**Preceptorships in Urology.** UCSF. By arrangement.

Continuously—**Training for Physicians in Nephrology.** CRMP Area VI and LLU at LLU. Courses of four weeks or more available, to be scheduled by arrangement. Hemodialysis, peritoneal dialysis, renal biopsy, and kidney transplantation. 160 hrs. Contact: Stewart W. Shankel, MD, LLU.

Continuously—**Surgical Anatomy.** St. Mary's Hospital, San Francisco. Mondays, 4:30 p.m., St. Mary's Hall, 2 W. Classroom. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Cline Clinic.** St. Mary's Hospital, San Francisco. Mondays, 1:30 p.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously—**Surgical Morbidity and Mortality Conference.** 4th Monday of each month, 9:00-10:00 a.m., Morrissey Hall. Contact: Charles H. Lithgow, MD, Dir. of Med. Ed., St. Mary's Hospital, 2200 Hayes St., San Francisco 94117. (415) 752-4000.

Continuously — **Surgical Pathology Conference.** See Radiology/Pathology, Continuously.

Continuously—**Thoracic Surgery Conference.** San Joaquin General Hospital, Stockton. Fourth Wednesday of each month, 9:00-10:30 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Medical Surgical Combined Conference.** San Joaquin General Hospital, Stockton. Second Wednesday of each month, 10:00-11:15 a.m., Conference Room 1. Contact: J. D. Kortzeborn, MD, Med. Dir., San Joaquin Gen. Hosp., Stockton 95201. (209) 982-1800.

Continuously—**Orthopaedic Audio-Synopsis Foundation.** A nonprofit service for Orthopaedic Surgeons publishing monthly recorded teaching programs which include summaries of pertinent literature and excerpts from national and international orthopaedic meetings. Monthly c-60 cassette tapes. Annual subscription rate $75 ($37.50 for residents). Contact: A. Harris, Man. Ed., OASF, 1510 Oxley St., So. Pasadena 91030. (213) 682-1760.

Grand Rounds—Surgery

Mondays

9-10 a.m., Morrissey Hall, St. Mary's Hosiptal, San Francisco.

Tuesdays

Orthopedic Surgery. 8:00 a.m., Sacramento Medical Center, Sacramento. UCD.

Urology. 7:30 a.m., Sacramento Medical Center, Sacramento. UCD.

8:30 a.m., Lebanon Hall Auditorium, Cedars-Sinai Hospital, Los Angeles. UCLA.

Wednesdays

7:15 a.m., Auditorium, Kern County General Hospital, Bakersfield. CRMP Area IV.

8:00-10:00 a.m., San Joaquin General Hospital, Stockton.

3:30 p.m., Sacramento Medical Center, Sacramento. UCD.

Thursdays

Neurology and Neurosurgery. 11:00-12:15, Room 663, Science Building, UCSF.

Fridays

1:00-2:00 p.m., Auditorium, Orange County Medical Center, Orange. UCI.

Neurosurgery. 9:30 a.m., held alternately at Stanford University Hospital and Neurology Conference Building 7, VA Hospital, Palo Alto. STAN.

Saturdays

8:00 a.m., Auditorium, 1st floor, University Hospital of San Diego County, San Diego, UCSD.

Urology. 8:00 a.m., 3rd floor conference room, University Hospital of San Diego County, San Diego. UCSD.

Orthopedics. 8:00-9:00 a.m. St. Mary's Hospital, San Francisco.

8:30 a.m., Assembly Room, Harbor General Hospital, Torrance. CRMP Area IV.

9:00 a.m., Room 73-105, Health Sciences Center, UCLA.

Orthopedics. 10:00 a.m. Auditorium of the Children's Division, Los Angeles County-USC Medical Center. The third Saturday of each month. USC.

OF INTEREST TO ALL PHYSICIANS

June 15—**Nutrition and the Physician.** UCLA. Saturday.

June 16-20—**1974 Birth Defects Conference.** See Pediatrics, June 16-20.

July 3-7—**Sexual Dysfunction.** UCLA at Residential Conference Center, Lake Arrowhead. Wednesday-Sunday.

July 14-20—**Management Seminar for University/College Health Services.** California Polytechnic State Univ., San Luis Obispo. Sunday-Saturday. $125. Contact: Mr. David Graham, Health Center, Calif. Polytechnic State Univ., San Luis Obispo 93407.

August 17-28—**Postgraduate Refresher Course—17th Annual.** USC at Hawaii. 12 days. $225.

August 21-24—**Family Practice Board Review.** UCLA at Beverly Hilton Hotel, Los Angeles. Wednesday-Saturday.

August 25-30—**Family Practice Refresher Course.** UCD at Squaw Valley. Sunday-Friday.

September 3-8—**Family Practice Review Course—5th Annual.** UCI. Tuesday-Sunday. 44 hrs.

September 11-14—**Life Saving Measures for the Critically Injured.** UCLA. Wednesday-Saturday.

September 21-22—**Acupuncture.** UCLA. Saturday-Sunday.

October 7-11—**Common Problems in Primary Care.** STAN. Monday-Friday. A review course for family physicians, gen. internists and gen. pediatricians.

October 10-12—**Western Industrial Health Conference—18th Annual.** Western Industrial Medical Association at Hilton Hotel, Los Angeles. Thursday-Saturday. Contact: Mr. B. H. Bravinder, Exec. Sec., P.O. Box 201, Alamo 94507. (415) 837-0874.

October 14-17—**American Academy of Family Physicians—Annual Scientific Assembly.** Los Angeles Convention Center. Monday-Thursday. Contact: Edward E. Daleske, Sec., Comm. on Scientific Programs, AAFP, 1740 W. 92nd St., Kansas City, Mo. 64114. (816) 333-9700.

October 28-November 1—**Intensive Care.** STAN. Monday-Friday.

October 29-November 1—**Hawaii Medical Association.** Ilikai Hotel, Honolulu. Tuesday-Friday. Contact: Mr. H. Tom Thorson, Exec. Dir., 510 S. Beretania St., Honolulu 96813.

Continuously—**Continuing Medical Education Noon Conferences.** The Hospital of the Good Samaritan, Los Angeles. Every weekday, 12-1 p.m. For monthly calendar, contact: Janie Sternal, Coord., Cont. Med. Ed., Hosp. of the Good Samaritan, 1212 Shatto St., Los Angeles 90029. (213) 482-8111.

Continuously—**Clinical Problems in Daily Practice: Physiological Basis and Practical Management.** UCSF at Chinese Hospital, San Francisco. 1st Tuesday of each month; 8:00-9:30 p.m. June—The Patient in Respiratory Failure; July—Diabetes Mellitus; Aug.—Congestive Heart Failure; Sept—Jaundice; Oct. & Nov.—to be announced.

Continuously—**Bedside Clinics.** See Medicine, Continuously.

Continuously—**Family Health Program—Southern California.** 2925 N. Palo Verde, Long Beach. Second Friday of each month. 1:00-2:00 p.m. Contact: UCI.

Continuously — **Lecture Program.** Riverside-San Bernardino Chapter, American Academy of Family Physicians and UCI at Ram's Horn Inn, San Bernardino. 3rd Thursday of each month. 7:30 p.m. Contact· UCI.

Continuously—**Lecture Program.** UCI and Orange County Chapter, American Academy of Family Physicians at Saddleback Inn, Santa Ana. 2nd Monday of each month, 7:30 p.m. Contact: UCI.

Continuously—**Hospital Lecture Program.** UCI at Anaheim Mem. Hosp.; Brea Comm. Hosp.; Fountain Valley Comm. Hosp.; Garden Park Gen. Hosp., Anaheim; Hartland Comm. Hosp., Baldwin Park; Huntington Intercomm. Hosp., Huntington Beach; Imperial Gen. Hosp., Inglewood; La Habra Comm. Hosp.; La Mirada Comm. Hosp.; La Palma Intercommunity Hosp., La Palma; Los Alamitos Gen. Hosp.; Mission Comm. Hosp., Mission Viejo; Palm Harbor Hosp., Garden Grove; Riviera Hosp., Torrance; Rio Hondo Mem. Hosp., Downey; San Gabriel Valley Comm. Hosp., San Gabriel; Stanton Comm. Hosp.; Studebaker Comm. Hosp., Norwalk; West Anaheim Gen. Hosp.; Westminster Comm. Hosp. Contact: UCI.

Continuously—**Professional Education Program.** Porterville State Hospital. Contact: Frank McCarry, MD, P.O. Box 2000, Porterville. (209) 784-2000.

Continuously—**Round Tables with Pacific Medical Center.** PMC and Sonoma Valley Hospital at Sonoma Valley Hospital, Sonoma. Second Monday of each month in Dining Room of the hospital, 8:00-10:00 p.m. $100 per series, $15 per session. Contact: William J. Newman, MD, P.O. Box B, Sonoma 95476. (707) 996-3621.

Continuously—**Basic Science Lecture Series.** UCSD Mondays, 4:00 p.m., third floor conference room, University Hospital of San Diego County, San Diego. Contact: UCSD.

Continuously—**Audio-Digest Foundation.** A non-profit subsidiary of CMA. Twice-a-month tape recorded summaries of leading national meetings and surveys of current literature. Services by subscription in: Family Practice, Surgery, Internal Medicine, Ob/Gyn, Pediatrics, Psychiatry, Anesthesiology, Ophthalmology, Otorhinolaryngology. Catalog of lectures and panel discussions in all areas of medical practice also available. $75 per year. Contact: Mr. Claron L. Oakley, Editor, Suite 700, 1930 Wilshire Blvd., Los Angeles 90057. (213) 483-3451.

Continuously—**Medical Media Network.** Programs and study guides produced in association with faculties of major medical schools and centers throughout the U.S. MMN administered by University Extension, UCLA. Rental or purchase, 16 mm, super 8 mm, videotape and video-cassette. Provides physicians with current educational programs. Contact: Ms. Jan MacAllister, Distribution Mgr., MMN, 10995 Le Conte Ave., Room 540, Los Angeles 90024. (213) 825-7781.

Continuously—**Stanford-Mills Memorial Hospital Continuing Education Program.** STAN at Mills Memorial Hospital, San Mateo. Tuesday-Friday weekly. Basic Science for the Clinician, Grand Rounds, Intensive Care. Contact: STAN.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 2164 S.W. Park Place, Portland, Oregon 97205; or phone (503) 226-1555.

OF INTEREST TO ALL PHYSICIANS

September 11-15—**Oregon Medical Association 100th Annual Session.** Portland Hilton Hotel. Contact: James Kronenberg, Associate Executive Director, OMA, 2164 SW Park Place, Portland 97205.

WASHINGTON, MONTANA, ALASKA and IDAHO

July 24-27—**Idaho Medical Association Annual Meeting.** Sun Valley. Contact: Armand L. Bird, Executive Director, IMA, 407 W. Bannock Street, Boise 83702. (208) 344-7888.

September 12-15—**Montana State Medical Association Annual Meeting.** Big Sky of Montana, Big Sky. Contact: G. Brian Zins, Executive Director, MSMA, 2021 11th Avenue—Suite 12, Helena 59601. (406) 443-4000.

September 22-25—**Washington State Medical Association Annual Meeting.** Davenport Hotel, Spokane. Contact: Harlan R. Knudson, Executive Director, WSMA, 444 NE Ravenna Boulevard—#108, Seattle 98115. (206) LA 3-9110.

REGIONAL MEDICAL PROGRAM

In order to have future activities listed here or to receive information on these and other activities, please write Ms. Joan M. Kelday, Information Specialist, Continuing Medical Education, WAMI Program, University of Washington School of Medicine, E-301, Health Sciences Building, SC-45, Seattle, Washington 98195. Phone: (206) 543-6995.

June 12-August 28—**Expo '74—Topics in Medicine.** Every Wednesday morning for 12 weeks. Deaconess Hospital, Spokane. 3 hrs. per session. $10 per session; $90 for 12 sessions. Contact Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305, HSB, SC-50, Seattle 98195. (206) 543-1050.

June 28-29—**Diagnosis and Management of Diffuse Pulmonary Infiltrates.** Friday-Saturday. Virginia Mason Medical Center Auditorium. 9 hrs. $35. Contact: Kenneth Wilske, MD, Dir. CME, Virginia Mason Medical Center, 1111 Terry Ave., Seattle 98101. (206) MA3-3700 ext. 470.

July 14-20—**Radiation Research Society, 22nd Annual Meeting.** Sunday-Saturday. Contact: R. J. Burk, Jr., 4211 39th St. NW, Washington, D.C. 20016.

July 25-27—**American Electroencephalographic Society.** Thursday-Saturday. Washington Plaza, Seattle. Contact: Mrs. Margaret H. Henry, 36391 Maple Grove Rd., Willoughby Hills, Ohio 44094.

July 29-31—**World of the Heart and Lung.** Monday-Wednesday. Seattle. Fee not set. Contact: Mr. Richard L. Reimer, Asst. Director, CME, Univ. of Wash. Sch. of Med., E-305, HSB, SC-50, Seattle 98195. (206) 543-1050.

Index to The Western Journal of Medicine Advertising

Ayerst Laboratories
Premarin 34, 35

Bio-Science Laboratories
Laboratory Service 36

Books Received 29

Breon Laboratories, Inc.
Bronkotabs 23

Burroughs Welcome Co.
Neosporin Ointment 25

Classified 30, 31

Compton Foundation 31

Dorsey Laboratories
Triaminic Expectorant ..... Back Cover

Eli Lilly & Company
Kefzol 24

Liberty Coin Company 29

Mead Johnson Laboratories
Vasodilan 16
Quibron Plus 28, 29

Medi-Fund Financial Corporation 20

McNeil Laboratories
Parafon Forte 38, 39

Obetrol Pharmaceuticals
Obetrol 15

Pharmaceutical Manufacturers Association
Prescription Ads 2, 3

AMA—123rd Annual Convention 10

Presto Food Products Inc.
Matey 9

Roche Laboratories
Librium ..... Inside Front Cover and Page 1
Bactrim 6, 7, 8
Efudex 18, 19
Dalmane 26, 27

Roerig (Pfizer)
Emete-con 11, 12, 13, 14

G. D. Searle & Co.
Pro-Banthine ..... 46 and 3rd Cover

Security Pacific Bank 5

State Compensation Insurance Fund 17

United States Air Force
Placement 22

Warner-Chilcott
Proloid 20, 21

Wyeth Laboratories
Bicillin/Wycillin 32, 33

how to civilize the of peptic ulcer...

give pain killers?...prescribe frequent eating?...use antacids only?

give pain killers only?

They relieve pain but may cause patient drug dependency and unnecessary sedation.

prescribe frequent eating only?

Frequent feeding helps buffer acid, but caloric, digestive, and social considerations make frequent eating both difficult and impractical.

use antacids only?

Antacids, like food, help neutralize or buffer stomach acidity. Their action is short, usually lasting only 1 to 1½ hours (given four hours after a meal).* Some patients may require antacids every half hour.

When you add Pro-Banthine® you

brand of
propantheline bromide

Indications: Pro-Banthine is effective as adjunctive therapy in the treatment of peptic ulcer. Dosage must be adjusted to the individual.

Contraindications: Glaucoma, obstructive disease of the gastrointestinal tract, obstructive uropathy, intestinal atony, toxic megacolon, hiatal hernia associated with reflux esophagitis, or unstable cardiovascular adjustment in acute hemorrhage.

Warnings: Patients with severe cardiac disease should be given this medication with caution.

Fever and possibly heat stroke may occur due to anhidrosis.

In theory a curare-like action may occur, with loss of voluntary muscle control. For such patients prompt and continuing artificial respiration should be applied until the drug effect has been exhausted.

Diarrhea in an ileostomy patient may indicate obstruction, and this possibility should be considered before administering Pro-Banthine.

Precautions: Since varying degrees of urinary hesitancy may be evidenced by elderly males with prostatic hypertrophy, such patients should be advised to micturate at the time of taking the medication.

Overdosage should be avoided in patients severely ill with ulcerative colitis.

Adverse Reactions: Varying degrees of drying of salivary secretions may

cannibal stomach

add Pro-Banthīne

Helps to relieve pain without risk of patient drug dependency.

add Pro-Banthīne

Reduces gastric secretory volume and total resting and free acid without the caloric, digestive, and social problems occasioned by frequent eating.

add Pro-Banthīne

Pro-Banthīne slows intestinal motility to enhance and prolong the action of antacids. The action of Pro-Banthīne lasts 4 to 6 hours.

*Fordtran, J. S., and Collyns, J. A. H.: Antacid Pharmacology in Duodenal Ulcer: Effect of Antacids on Postcibal Gastric Acidity and Peptic Activity, New England J. Med. 274:921-927 (April 28) 1966.

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Address medical inquiries to: G. D. Searle & Co. Medical Department, Box 5110, Chicago, Ill. 60680

usually get better patient response.

ccur as well as mydriasis and blurred vision. In addition the following dverse reactions have been reported: nervousness, drowsiness, dizziness, nsomnia, headache, loss of the sense of taste, nausea, vomiting, constipa- on, impotence and allergic dermatitis.

Dosage and Administration: The recommended daily dosage for adult ral therapy is one 15-mg. tablet with meals and two at bedtime. Subse- uent adjustment to the patient's requirements and tolerance must be nade.

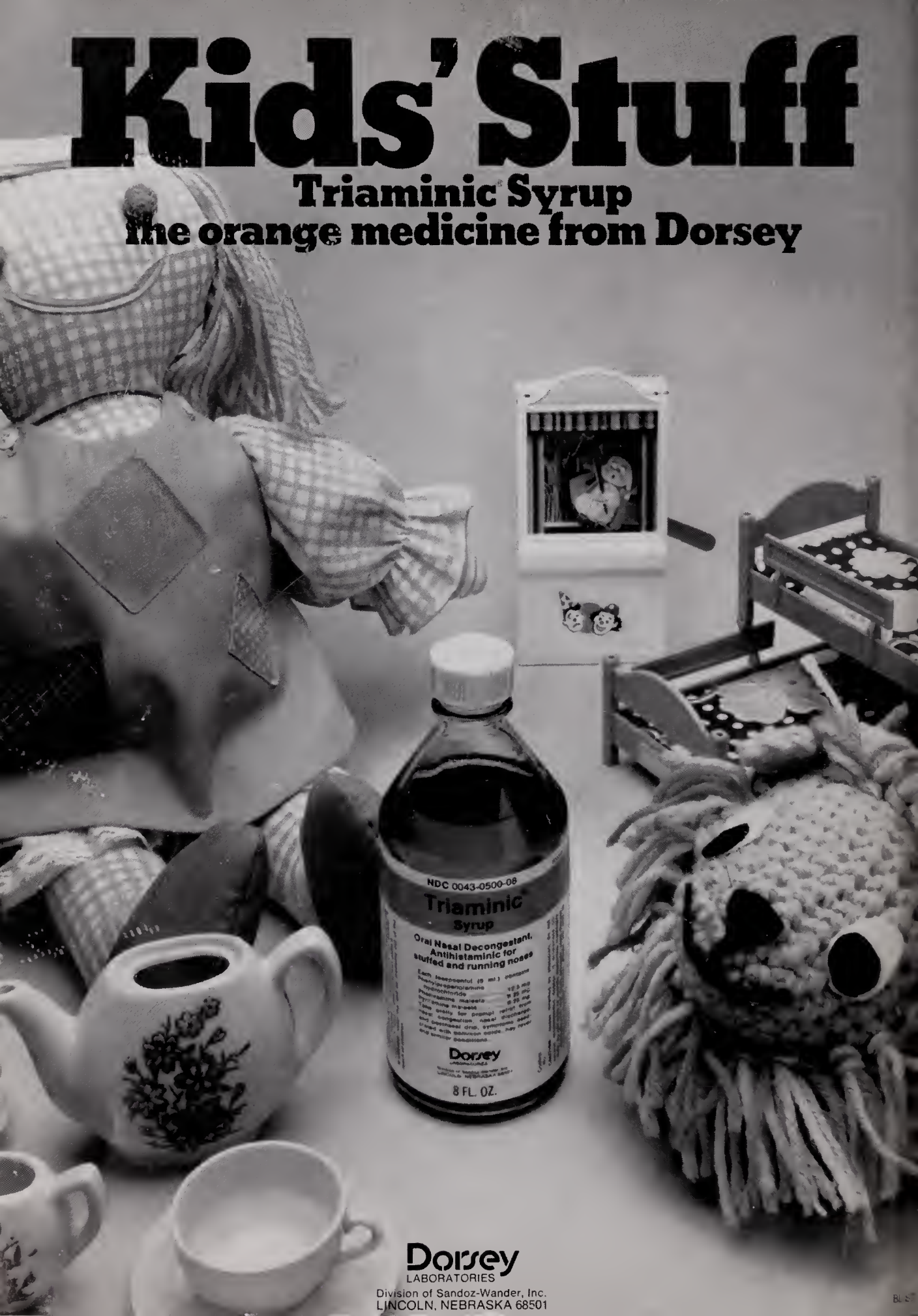
ro-Banthīne P.A.—Each tablet of Pro-Banthīne P.A. (propantheline romide) contains 30 mg. of the drug in the form of sustained-release or timed-release beads; on ingestion about half of the drug is released within an hour and the remainder continuously as earlier increments are metabolized. Thus the result is even, high-level anticholinergic activity maintained all day and all night in most patients with only two tablets daily. Some patients may require one tablet every eight hours.

The contraindications and precautions applicable to Pro-Banthīne 15 mg. should be observed.

How Supplied: Pro-Banthīne is supplied as tablets of 15 and 7.5 mg., as prolonged-acting tablets of 30 mg. and, for parenteral use, as serum-type vials of 30 mg.

Kids' Stuff

Triaminic Syrup
the orange medicine from Dorsey



Dorsey
LABORATORIES
Division of Sandoz-Wander, Inc.
LINCOLN, NEBRASKA 68501